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Oral and Maxillofacial Medicine

**The Basis of Diagnosis
and Treatment**



Crispian Scully

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ORAL AND MAXILLOFACIAL MEDICINE

The Basis of Diagnosis and Treatment

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Development Editor: Hannah Kenner

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Illustrator: Dartmouth Inc.

Illustration Manager: Gillian Richards

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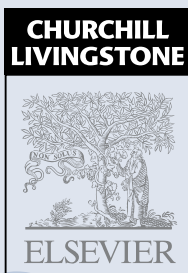
Crispian Scully

CBE MD PhD MDS MRCS FDSRCS FDSRCPS FFDRCSI FDSRCSE FRCPath FmedSci
FHEA DSc

*Dean and Director of Studies and Research, and Professor of Oral Medicine,
Pathology and Microbiology, University of London, UK*

*Eastman Dental Institute, and WHO Collaborating Centre for Disability, Culture
and Oral Health, University College London, UK*

*Visiting Professor at Universities of Edinburgh, Helsinki, Middlesex and West of
England; Honorary Consultant at University College Hospitals, London, UK;
Great Ormond Street Hospital, London;
and European Institute for Oncology, Milan, Italy*



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Note

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Author assume any liability for any injury and/or damage to persons or property arising out or related to any use of the material contained in this book.

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Preface to second edition

I am pleased to say that the first edition was very well received and proved popular. Indeed, the book was awarded the First Prize of the Royal Society of Medicine and Society of Authors, for a new authored book.

Nevertheless, I have taken the opportunity to re-structure; to thoroughly revise and update the text; to reformat where this could enhance clarity; to add new material and clinical pictures and some basic histopathology, tables, boxes and algorithms; to add new chapters on sialorrhoea and drooling, other conditions, and adverse drug reactions; and to update Further Reading.

My additional thanks are to John Huw Evans for his technical assistance, to Dr Stefano Fedele for his

comments overall, to Dr Mohamed El-Maaytah and Dr Navdeep Kumar for providing a few figures, to Professor John Eveson for kind permission to use histopathology from our book Eveson, J.W. and Scully C. *Colour Atlas of Oral Pathology* (1995). Mosby-Wolfe (London) and to Peter Reichart, David Sidransky and Dr L. Barner for permission to reproduce their WHO Classifications from Pathology and Genetics of Tumours of the Head and Neck (2005) and to Professor Mervyn Shear for commenting on the chapter on Odontogenic Cysts and Tumours.

CS
2007

The wise should consider that health is the greatest of human blessings.

Hippocrates

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Preface to first edition

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Oral medicine is that area of special competence in dentistry concerned mainly with diseases involving the oral and perioral structures, especially the oral mucosa, and the oral manifestations of systemic diseases. The specialty, in some countries termed 'stomatology', deals not only with oral disease but also with perioral lesions, and is increasingly known as 'oral and maxillofacial medicine'. Furthermore, apart from the obvious close relationships with oral pathology (oral and maxillofacial pathology) and with oral surgery (oral and maxillofacial surgery), there is a close relationship with special care dentistry and hospital dentistry.

This book attempts to present for those interested in oral medicine and hospital dentistry, the basics of the specialty of oral medicine in a useful and digestible format; by offering the information in a range of modes and levels of detail and offering practical guidance to diagnosis, therapy and sources of information for patient and clinician, both on the Internet and elsewhere.

The first section reviews the fundamental principles of the history, examination and investigations and principles of management. In the absence of randomized controlled trials, many of the therapies suggested are unable to be thoroughly evidence based. Hopefully, future multicentre studies will rectify this deficiency. The second section discusses the more common symptoms and signs in oral medicine.

The third section covers in some detail the most common and important conditions seen in oral medicine. This section also includes synopses of a number of eponymous and other conditions relevant to oral medicine; if a specific condition is not found there, the reader is referred to the index, since it may well be located elsewhere in the book.

The fourth section is a discussion of the important areas of HIV infection and iatrogenic diseases.

The other relevant oral manifestations of systemic disorders are tabulated in Appendix 1: further detail can be found in *Medical Problems in Dentistry* (Scully and Cawson: Elsevier, Edinburgh, 2004).

Agents used in the treatment of patients with oral diseases are outlined in Appendix 2. Only a limited number of these are prescribed by dental practitioners, but practitioners may have to cope with questions from patients about their treatment, or to recognize or deal with treatment complications. Further details can be found in textbooks such as *Basic Pharmacology and*

Clinical Drug Use in Dentistry (Cawson, Spector and Skelly: Churchill Livingstone, Edinburgh, 1995).

An attempt has been made to present the material in such a way as to highlight the more important conditions – important because of frequency or seriousness – and to guide the reader through didactic and problem-oriented approaches. However, it is impossible to position every subject in a perfect location, not least because few conditions affect only one site (e.g. even erythema migrans can have lesions in sites other than on the tongue), some affect even more than one tissue (e.g. ectodermal dysplasia affects skin, salivary glands and teeth) and several have a range of clinical presentations (e.g. lichen planus and cancer can both present with white, red or ulcerative lesions, and can be symptomless or cause extreme discomfort). Cross-referring between sections will help the user get full value from the content.

The book is not intended to give all the details of the various investigative and therapeutic modalities, since these are covered in other texts by the author, or in pharmacopoeias. The book offers illustrative examples of the more common and important conditions, but cannot provide the more comprehensive selection of illustrations such as can be found in atlases such as *Oral Diseases* (Scully, Flint, Porter and Moos: Dunitz, London, 2004).

I thank my patients and nurses who have taught me so much over the years, and continue so to do, and all those students and colleagues with whom I have worked and interacted, who may have shared the clinical care of some patients, and/or may have knowingly or otherwise contributed ideas or content. In this respect I thank especially Professors Oslei Almeida (Brazil), Jose-Vicente Sebastian-Bagan (Spain), Johann Beck-Managetta (Austria), Roman Carlos (Guatemala), Marco Carrozzo (Italy), Roderick Cawson (UK), Pedro Diz Dios (Spain), Dore Eisen (USA), Joel Epstein (Canada), Sergio Gandolfo (Italy), George Laskaris (Greece), Jens Pindborg (Denmark; deceased), Stephen Porter (UK), Peter Reichart (Germany), Pierre-Luigi Sapelli (Italy), Sol 'Bud' Silverman (USA) and Isaac Van der Waal (The Netherlands).

Thanks are also due to: Alan Drinnan (USA) for his innovative introduction of the Bulletin Board in Oral Pathology (BBOP), a useful world forum for oral medicine and pathology; to Miguel Lucas-Tomas (Spain), who founded the European Association for

Preface to first edition

Oral Medicine – a major European forum; and to Dean Millard (USA) and David Mason (UK), who had the foresight to institute the World Workshops in Oral Medicine; to John Greenspan (USA) who had the foresight to organize the Oral AIDS workshops; and to Newell Johnson with whom I founded and co-edit Oral Diseases. These giants have helped the progression of oral medicine to the high level at which it now stands.

Much of my work could not be done without the support of my family (Zoe and Frances) and my work colleagues who help with information collection,

particularly John Evans, Avril Gardner, Lesley Garlick and Karen Widdowson, to whom thanks are due. I thank Jose-Vicente Sebastian Bagan and Isaac van der Waal, and also my nephew, Dr Athanassios Kalantsis, for their helpful, friendly and constructive comments on the text.

Finally, I would be delighted to receive any comments about this text, in the hope that I can improve further in the future.

CS

London 2003

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Intended outcomes

This text will deal with oral and maxillofacial diseases and their medical management, and it is intended that, having read this text, the reader will be able to:

- Adopt a systematic approach to medical history taking that extends routine questions into certain relevant areas of enquiry that involve the body in general.
- Examine patients and their oral lesions systematically and use the findings of specific features of the lesion and associated signs and symptoms, to start formulating differential diagnoses.
- Identify which sites may be affected by the presenting condition and what to look for at those sites.
- Identify relevant follow-up questions that may further clarify the findings of the clinical examination and refocus the history.
- Understand when clinical investigations are indicated, which are appropriate, and how to perform these investigations.
- Interpret the findings of routine clinical investigations (e.g. blood test results) and develop a sense of the potential implications for the patient.
- Recognize the scope of oral and maxillofacial diseases and the importance of medical management in addition to the traditional dental focus of the discipline.
- Advise the patient about the aetiology of oral lesions, and predisposing factors.
- Identify lesions and interpret the findings and develop a sense of the potential implications for the patient.
- Identify a range of therapeutic options for the patient and understand the need for regular review and re-appraisal of the condition.
- Understand how treatment may impact, positively or negatively, upon the condition.
- Identify the need to refer for advice, investigations or treatment by dental, medical or surgical specialists.
- Recognize the importance of close liaison with colleagues in other disciplines, particularly medicine, pathology and surgery.

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SECTION 1

FUNDAMENTAL

PRINCIPLES OF PATIENT

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1

Diagnosis: history

It is better to know what kind of patient has the disease than what kind of disease the patient has.

Sir William Osler

Introduction

Diagnosis means ‘through knowledge’ and entails acquisition of data about the patient and their complaint using the senses:

- observing
- hearing
- touching
- sometimes smelling (Fig 1.1).

The purpose of making a diagnosis is to be able to offer the most:

- effective and safe treatment
- accurate prognostication.

Diagnosis is made by the clinical examination, which comprises the:

- history (anamnesis) – this offers the diagnosis in about 80% of cases
- physical examination
- supplemented in some cases by investigations.

Each is based on a thorough, methodical routine. Diagnosis most importantly involves a careful history; the patient will often deliver the diagnosis from the history, though the findings from examination and investigations can be helpful. To state the obvious, it is difficult to diagnose a condition that is unknown to the diagnostician; thus extensive reading of recent literature, clinical experience and discussion with colleagues is continually needed, as well as an enquiring mind. Continuing education is essential.

There are many types of diagnosis (Box 1.1), including:

- Clinical diagnosis: made from the history and examination.
- Pathological diagnosis: provided from the pathology results.
- Direct diagnosis: made by observing pathognomonic features. This is occasionally possible, for example in dentinogenesis imperfecta where the abnormally translucent brownish teeth are characteristic.
- Provisional (working) diagnosis: the more usually made diagnosis. This is an initial diagnosis from which further investigations can be planned.

Listen		History Speech
Observe		Appearance Behaviour
Touch		Induration Temperature
Smell		Malodour

Fig. 1.1 The senses in diagnosis

- Deductive diagnosis: made after due consideration of all facts from the history, examination and investigations.
- Differential diagnosis: the process of making a diagnosis by considering the similarities and differences between similar conditions.
- Diagnosis by exclusion: identification of a disease by excluding all other possible causes.

► Box 1.1

Types of diagnosis

- Clinical diagnosis
 - Diagnosis ex-juvantibus
 - Differential diagnosis
 - Pathological diagnosis
 - Direct diagnosis
 - Provisional (working) diagnosis
 - Deductive diagnosis
 - Diagnosis by exclusion
 - Provocative diagnosis: induction of a condition to establish diagnosis
- Diagnosis ex-juvantibus: made on the results of response to treatment. For example, the pain of trigeminal neuralgia may be atypical, and the diagnosis can sometimes be confirmed only by a positive response to the drug carbamazepine.
 - Provocative diagnosis: the induction of a condition in order to establish a diagnosis. This is rarely needed, except in possible drug reactions or allergies, when the patient may need to be re-exposed to the potentially culpable substance, but this should always be carried out where appropriate medical support and resuscitation are available.

History taking

The first contact with the patient is crucial to success and there should be a courteous approach to the patient with a professional introduction and every effort to establish communication, rapport and trust, and make the patient feel the focus of the clinician's interest. History taking is part of the initial communication between the dentist and patient. It is important to adopt a professional appearance and manner, and introduce oneself clearly and courteously. The patient will know if you care, well before they care if you know.

The clinician should encourage the patient to tell the story in their own words, and use methodical questioning to elucidate further details.

Perhaps not surprisingly, many patients are apprehensive when confronted by a clinician, and therefore they may be easily disturbed if, for example, the clinician appears indifferent or unsympathetic. This can result in barriers to effective communication, which will simply hinder the clinician.

Due cognizance must also always be taken of the age, cultural background, understanding and intelligence of the patient when taking the history. It is the clinician's

responsibility to elicit an accurate history; if that necessitates finding an interpreter, for example, then the clinician must arrange this.

The history is best given in the patient's own words, though the clinician often needs to guide the patient, and may use protocols to ensure collection of all relevant points.

It is important to cover the following areas:

- general information (name, date of birth, gender, ethnic origin, place of residence, occupation)
- presenting complaint
- history of the present complaint
- past medical history
- dental history
- family history
- social and cultural history
- patient expectations.

By the end of the history, the clinician should have an idea of the patient's concerns, have assessed the patient's current problems and also have drawn up a provisional or differential diagnosis.

Presenting complaint

The history taking commences by identifying the current complaint(s), e.g. 'sore mouth'. The 'history of the present complaint' is then taken.

History of the present complaint

This should cover aspects relevant to the particular main complaint, such as:

- date of onset
- duration
- location(s)
- aggravating and relieving factors
- investigations thus far
- treatment already received.

'Leading questions' (i.e. those which suggest the answer) should be avoided. 'Open questions', which do not suggest an answer, are preferred. The history should be directed by the complaint. Then a series of relevant questions should elicit the 'past or relevant medical history'.

Past or relevant medical history

The medical history should be taken to elicit all matters relevant to the:

- diagnosis
- treatment
- prognosis.

As a double check on the verbal history, the use of pre-printed, standardized, self-administered questionnaires is helpful, and may encourage more truthful responses to sensitive questions.

The history should uncover, for example, medical history relevant to:

- Previous episodes of similar or related complaints.
- Other complaints that may be relevant. For example, in patients with mucosal disorders, it is important to ascertain whether there have been lesions affecting other mucosae (ocular or anogenital) or skin.

Important to include are:

- General symptoms, such as fever or weight loss.
- Relevant symptoms related to body systems, such as:
 - nervous system (e.g. sensory loss)
 - respiratory system (e.g. cough)
 - gastrointestinal disorders that may be associated with oral ulcers and other lesions
 - skin lesions (solitary or rashes), itch or discolourations, which are common symptoms of skin disease, and there are sometimes oral lesions
 - ocular problems or visual disturbance
 - anogenital lesions, such as ulcers or warts
 - psychiatric disorders, such as anxiety, depression and eating disorders, and drug abuse are relevant to orofacial conditions.
- Medical or surgical consultations, investigations and treatments, including radiotherapy.
- Current prescribed drugs (including self-medications and alternative medicines), since these may cause oral complaints or influence management.
- Complementary medicine.
- Allergies.
- Previous illnesses.
- Hospitalizations and previous consultations.
- Operations.
- Anesthetics.
- Specific medical problems that may influence operative procedures, particularly:
 - bleeding tendency
 - corticosteroid therapy
 - diabetes
 - cardiac problems
 - endocarditis risk.

Patients may also carry formal warnings of certain conditions relevant to dental care. These may be written cards, smart cards, bracelets or necklaces. Some may bring quite precise written information (Fig 1.2).

The medical history of dental patients should be directed to elicit any relevant systemic disease. For example, this may be achieved by an ABC:

- Anaemia: a reduction in haemoglobin level below the normal for age and sex. It can:
 - be a contraindication to general anaesthesia

- cause oral complications (i.e. candidiasis, sore mouth, burning tongue, glossitis, ulcers, angular stomatitis).
- Bleeding tendency: a hazard to any surgical procedure, including some injections, and a contraindication to aspirin and some other non-steroidal anti-inflammatory drugs (NSAIDs).
- Cardiorespiratory disease: this may be a contraindication to general anaesthesia. Patients with various cardiac lesions are predisposed to develop endocarditis, which may be precipitated as a consequence of the bacteraemia associated with some forms of dental treatment. Cardiac patients may need antimicrobial cover to prevent infective endocarditis or may have a bleeding tendency because of anticoagulants.
- Drug use, allergies and abuse: these may cause orofacial lesions or give an indication about underlying pathology, or may influence dental procedures or drug use. Drug allergies are a contraindication to the use of the responsible or related drugs. Drug abuse may give rise to behavioural problems and a risk of cross-infection. Corticosteroids absorbed systemically produce adrenocortical suppression. Such patients may not respond adequately to the stress of trauma, operation or infection, and stress may produce adrenal crisis and collapse.
- Endocrine disease.
 - Diabetes may cause:
 - the danger of hypoglycaemia if meals are interfered with
 - oral complications such as sialosis, dry mouth and periodontal breakdown.
 - Hyperparathyroidism may cause:
 - jaw radiolucencies/rarefaction
 - loss of lamina dura
 - giant cell granulomas (central)
 - hypercalcaemia.
- Fits and faints: epilepsy and other causes of unconsciousness should be elicited before embarking on any procedures. Oral lesions may be seen.
- Gastrointestinal disorders: are relevant mainly because of possible vomiting with general anaesthesia, and possible oral manifestations.
- Hospital admissions, attendances and operations: this information often helps fill in gaps in the medical history, and may be relevant if, for example, the patient has had a previous halothane anaesthetic or has had radiotherapy. Surgery in the absence of any serious postoperative haemorrhage also suggests the absence of any inherited bleeding tendency.
- Infections: the possibility of transmission of infection to patients or staff is ever present:
 - blood-borne infections – hepatitis viruses B and C, and HIV are the main agents of concern
 - respiratory infections – current or very recent respiratory infections, particularly tuberculosis, may be transmissible and a contraindication to general anaesthesia

CONDITION	DESCRIPTION	NO. OF PILLS	MG	PERIOD	ON Prescrtn.	CONTENTS
Blood pressure	COSAAR	2	50	ONCE DAILY		Losarton potassium
	PLAVIX	1	75	ONCE DAILY		Clopidogrel hydrogen sulpt.
For cholesterol	BEZALIP MONO	1	400	ONCE DAILY		Bezafibrate
(From 19-03-04)						Lactose povidone
						Sodium lauryl sulphate
						Hydroxypropyl
						Methylcellulose
						Colloidal silicon dioxide
						Magnesium stearate
						Polymethacrylic acid eaters
						Polyethylene glycol. talc
						Titanium dioxide (E171)
						Polysorbate 80
						Sodium dilate dihydrate
	BENECOL	Yogurt	2g	ONCE DAILY		Plant stanol
For back pain	PARACETAMOL	2	500	3 TIMES DAILY		Maize starch stearic acid
	OMERPROZOLE	1	20	ONCE DAILY		
	ASPIRIN	1	75	ONCE DAILY		
Anxiety	OXAZEPAM	1	10	ONCE DAILY		Lactose, maize starch
STOPPED						and magnesium stearate
For tremor	INDERAL	1	10	ONCE DAILY		Propranolol hydrochloride
STOPPED						Ph eur and glycerol
Sleep	ZIMOVANE	1	7.5	ONCE A NIGHT		Zopiclone
Sleep	DIAZEPAM	1	5	ONCE A NIGHT		Lactose, maize starch
						Magnesium stearate
						Colloidal silicon dioxide
						Sodium starch glycol-ate
						and tartrazine lake
For IBS when required	BUSCOPAN	2	10	3 TIMES DAILY		Hyoscine butyltoromide
For IBS when required	COLOFAC	1		Before a meal		Medeverine hydrochloride

Fig. 1.2 Medical history sheet given by a fastidious patient

- sexually transmitted infections – imprecise diagnosis or empirical treatment serves only to spread these infections, as contact tracing is normally undertaken only on proven cases of sexually transmitted (venereal) disease.
 - Jaundice and liver disease: these are important because of the associated bleeding tendency, drug intolerance and possible viral hepatitis and oral carcinoma.
 - Kidney disease: this may cause a bleeding tendency and impaired drug excretion. The other main problems are in relation to the immunosuppression created following a kidney transplant, liability to neoplasia, and gingival swelling from ciclosporin.
 - Likelihood of pregnancy: because of the danger of abortion or teratogenicity, it is important during pregnancy, particularly the first trimester, to avoid or minimize exposure to drugs, radiography and infections. Pregnancy can influence some conditions such as aphthae pyogenic granulations and Behçet syndrome, and may produce gingivitis or epulides.
 - Malignant disease, including those on radiotherapy or chemotherapy (where oral lesions may occur): malignant disease may underlie some oral complaints, such as pain or sensory changes and can result in significant morbidity and even mortality.
 - Prosthesis and transplant patients: patients after transplants may be at risk from infection, neoplasms and iatrogenic problems, such as bleeding, gingival swelling or graft-versus-host disease. Patients with transplants are also liable to present a number of complications to dental treatment – in particular the need for a corticosteroid cover, a liability to infection and a bleeding tendency. There is no good evidence for infection of prosthetic joints arising from oral sepsis. However, if the orthopaedic surgeon wishes an antimicrobial cover, the dentist must consider the medicolegal implications.
- The complications of infection of ventriculo-atrial valves are so serious that, although as in the case of prosthetic

joints there is little evidence for an oral source, it may be reasonable to give an antimicrobial cover, if the responsible neurosurgeon so advises. Patients with pacemakers may be in danger in relation to the use of equipment, which can interfere with their pacemaker, such as diathermy and electrosurgery.

- Other relevant conditions: every condition which is elicited from the medical history should be checked for relevance, but the following can be highly relevant:
 - Down syndrome – there are many oral problems and cervical spine involvement may predispose to spinal cord damage during general anaesthesia
 - glucose-6-phosphate dehydrogenase deficiency is a contraindication to some drugs
 - hereditary angioedema – any dental trauma may result in oedema and a hazard to the airway
 - malignant hyperthermia (malignant hyperpyrexia) – various general anaesthetics and other agents may be contraindicated
 - porphyria – intravenous barbiturates, metronidazole and other agents may be contraindicated
 - rheumatoid arthritis – cervical spine involvement may predispose to spinal cord damage if the neck is

flexed during general anaesthesia; Sjögren syndrome is a common complication

- suxamethonium sensitivity – suxamethonium is contraindicated.

Dental history

The dental history will give an idea of the:

- regularity of attendance for dental care
- attitude to dental professionals and to treatment
- recent relevant dental problems
- recent restorative treatment.

Family history

This may reveal hereditary problems, such as amelogenesis imperfecta, haemophilia or hereditary angioedema, and familial conditions, such as recurrent aphthous stomatitis or diabetes. Some diseases are more prevalent in certain ethnic groups, e.g. pemphigus in Jews; Behçet's disease in people from the Mediterranean area.

► Box 1.2

Systematic recording of relevant medical history

System*	Specific problems	No	Yes
CVS	Heart disease, hypertension, angina, syncope Cardiac surgery, rheumatic fever, chorea Bleeding disorder, anticoagulants, anaemia		
RS	Asthma, bronchitis, TB, other chest disease, smoker		
GU	Renal, urinary tract or sexually transmitted disease Pregnancy, menstrual problems		
GI/Liver	Coeliac disease, Crohn's disease Hepatitis, other liver disease, jaundice		
CNS	CVA, multiple sclerosis, other neurological disease Psychiatric problems, drug or alcohol abuse Sight or hearing problems		
LMS	Bone, muscle or joint disease		
Endocrine	Diabetes, thyroid, other endocrine disease		
Allergy	Allergies – e.g. penicillin, aspirin, plaster		
Drugs	Recent or current drugs/medical treatment Corticosteroids, anticoagulants		
Others	Previous operations, general anaesthesia (GA) or serious illness Other conditions (including congenital anomalies) Family medical history Born, residence or travel abroad Pets		

*CVS: cardiovascular; RS: respiratory; GU: genitourinary; GI: gastrointestinal; CNS: central nervous system; LMS: locomotor system.

Social and cultural history

The social history may reveal:

- whether the patient has family or a partner and the degree of support that can be anticipated
- information about the patient's residence, which can suggest the socioeconomic circumstances of the patient
- information about contacts with pets and other animals, which may be relevant to some infectious diseases, such as cat-scratch disease or toxoplasmosis
- whether the patient has traveled overseas, which may be relevant to some infectious diseases, such as tropical diseases and deep mycoses
- the patient's sexual history, which may be relevant to some infectious diseases, such as human immunodeficiency virus (HIV), herpes simplex virus (HSV), papillomavirus (HPV) and hepatitis viruses A (HAV), B (HBV) and C (HCV)
- any occupational problems, which may be relevant to some disease, and access to care
- relevant habits (tobacco, alcohol, betel and recreational drug use) – tobacco use underlies several oral diseases, including periodontal disease and cancer
- relevant hobbies, such as swimming that may cause tooth erosion or scuba diving that may underlie temporomandibular pain

- information about the patient's diet – dietary fads may lead, for example, to vitamin deficiencies and glossitis or angular cheilitis (as in vitamin B₁₂ deficiency in vegans)
- information about stress.

Standardized forms will help with the recording of data, the relevance of which can sometimes be surprising (Box. 1.2).

Patient expectations can only be assessed by polite enquiry. Each patient is an individual with their own specific thoughts and beliefs.

Further reading

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2

Diagnosis: examination

The patient will know if you care, well before they care if you know.

Anonymous

Introduction

The clinical examination of the patient should start as the patient enters the clinic and is greeted by the clinician. The history and clinical examination are designed to put the clinician in a position to make a provisional diagnosis, or a differential diagnosis. Special tests or investigations may be required to confirm or refine this diagnosis or elicit other conditions. Physical disabilities, such as those affecting gait, and learning disability are often immediately evident as the patient is first seen, and blindness, deafness or speech and language disorders may be obvious. You should also be able to assess the patient's mood and general wellbeing but, if in any doubt, ask for advice. Other disorders, such as mental problems, may become apparent at any stage. The patient should be carefully observed and listened to during history taking and examination; speech and language can offer a great deal of information about the medical and mental state. As a general rule, if you think a patient looks ill, they probably are.

Always remember that the patient has the right to refuse all or part of the examination, investigations or treatment. A patient has the right under common law to give or withhold consent to medical examination or treatment. This is one of the basic principles of healthcare. Patients are entitled to receive sufficient information in a way they can understand about the proposed investigations or treatments, the possible alternatives and any substantial risk or risks, which may be special in kind or magnitude or special to the patient, so that they can make a balanced judgment (UK Health Department, 19.2.99. HSC 1999/031),

There may be cultural sensitivities but, in any case, no examination should be carried out in the absence of a chaperone – preferably of the opposite sex to the practitioner.

General examination

Medical problems may manifest in the fully clothed patient with abnormal appearance or behaviour, pupil size, conscious level, movements, posture, breathing, speech, facial

colour, sweating or wasting. General examination may sometimes include the recording of body weight and the 'vital signs' of conscious state, temperature, pulse, blood pressure and respiration. The dentist must be prepared to interpret the more common and significant changes.

Vital signs

- The conscious state.
- The temperature: the temperature is traditionally taken with a thermometer, but temperature-sensitive strips and sensors are available. Leave the thermometer in place for at least 3 minutes. The normal body temperatures are: oral 36.6°C; rectal or ear (tympanic membrane) 37.4°C; and axillary 36.5°C. Body temperature is usually slightly higher in the evenings. In most adults, an oral temperature above 37.8°C or a rectal or ear temperature above 38.3°C is considered a fever. A child has a fever when ear temperature is 38°C or higher.
- The pulse: this can be measured manually or automatically (Fig. 2.1). The pulse can be recorded from any artery, but in particular from the following sites:
 - the radial artery, on the thumb side of the flexor surface of the wrist
 - the carotid artery, just anterior to the mid-third of the sternomastoid muscle
 - the superficial temporal artery, just in front of the ear.
- Pulse rates at rest in health are approximately as follows:
 - infants, 140 beats/minute
 - adults, 60–80 beats/minute.



Fig. 2.1 Pulse meter



Fig. 2.2 Sphygmomanometer

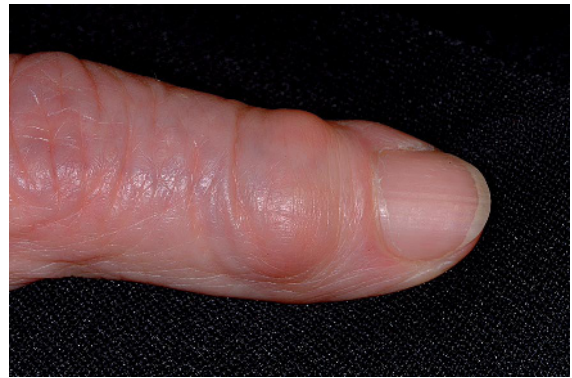


Fig. 2.4 Heberden's nodes of osteoarthritis



Fig. 2.3 Raynaud's syndrome in scleroderma

- Pulse rate is increased in:
 - exercise
 - anxiety or fear
 - fever (pyrexia)
 - some cardiac disorders
 - hyperthyroidism and other disorders.
- The rhythm should be regular; if not, ask a physician for advice. The character and volume vary in certain disease states and require a physician's advice.
- The blood pressure: this can be measured with a sphygmomanometer (Fig. 2.2), or one of a variety of machines. With a sphygmomanometer the procedure is as follows: seat the patient; place the sphygmomanometer cuff on the right upper arm, with about 3cm of skin visible at the antecubital fossa; palpate the radial pulse; inflate the cuff to about 200–250mmHg or until the radial pulse is no longer palpable; deflate the cuff slowly while listening with the stethoscope over the brachial artery on the skin of the inside arm below the cuff; record the systolic pressure as the pressure when the first tapping sounds appear; deflate the cuff further until the tapping sounds become muffled (diastolic pressure); repeat; record the blood pressure as systolic/diastolic pressures (normal values about 120/80mmHg, but these increase with age).



Fig. 2.5 Cerebral palsy

Other signs

- Weight: weight loss is seen mainly in malnutrition, eating disorders, cancer, HIV disease, malabsorption and tuberculosis. Obesity is usually due to excessive food intake and insufficient exercise.
- Hands: conditions, such as arthritis (mainly rheumatoid or osteoarthritis) (Figs 2.3 and 2.4) and Raynaud's phenomenon, which is seen in many connective tissue diseases. Disability, such as in cerebral palsy (Fig. 2.5).



Fig. 2.6 Clubbing

- Skin: lesions, such as rashes – particularly blisters (seen mainly in skin diseases, infections and drug reactions), pigmentation (seen in various ethnic groups, Addison's disease and as a result of some drug therapy).
- Skin appendages: nail changes, such as koilonychia (spoon-shaped nails), as seen in iron deficiency anaemia, hair changes, such as alopecia, and finger clubbing (Fig. 2.6), as seen mainly in cardiac or respiratory disorders. Nail beds may reveal the anxious nature of the nail-biting person (Fig. 2.7)

Extraoral head and neck examination

The face should be examined for lesions (Box 2.1) and features such as:

- pallor, seen mainly in the conjunctivae or skin creases in anaemia
- rash, such as the malar rash in systemic lupus erythematosus
- erythema, seen mainly on the face in an embarrassed patient, or fever (sweating or warm hands), and then usually indicative of infection. Malar erythema may indicate mitral valve stenosis.

Eyes should be examined for features such as:

- exophthalmos (prominent eyes), seen mainly in Graves thyrotoxicosis
- jaundice, seen mainly in the sclerae in liver disease



Fig. 2.7 Nail biting

- redness, seen in trauma, eye diseases, or Sjögren syndrome
- scarring, seen in trauma, infection or pemphigoid.

Inspection of the neck, looking particularly for swellings or sinuses, should be followed by careful palpation of all cervical lymph nodes and salivary and thyroid glands, searching for swelling or tenderness. The neck is best examined by observing the patient from the front, noting any obvious asymmetry or swelling, then standing behind the seated patient to palpate the lymph nodes. Most of the physical examination is undertaken from behind (Fig. 2.8). Systematically, each region needs to be examined lightly with the pulps of the fingers, trying to roll the lymph nodes against harder underlying structures:

Lymph from the superficial tissue of the head and neck generally drains first to groups of superficially placed lymph nodes, then to the deep cervical lymph nodes (Figs. 2.9–2.11 and Box 2.2).

- Parotid, mastoid and occipital lymph nodes can be palpated simultaneously using both hands.
- Superficial cervical lymph nodes are examined with lighter fingers as they can only be compressed against the softer sternomastoid muscle.
- Submental lymph nodes are examined by tipping the patient's head forward and rolling the lymph nodes against the inner aspect of the mandible.
- Submandibular lymph nodes are examined in the same way, with the patient's head tipped to the side which is being examined. Differentiation needs to be made between the submandibular salivary gland and submandibular lymph glands. Bimanual examination with one finger in the floor of the mouth may help.
- The deep cervical lymph nodes which project anterior or posterior to the sternomastoid muscle can be palpated. The jugulodigastric lymph node in particular should be specifically examined, as this is the most common lymph node involved in tonsillar infections and oral cancer.

► Box 2.1

The commoner descriptive terms applied to lesions

Term	Meaning
Atrophy	Loss of tissue with increased translucency, unless sclerosis is associated
Bullae	Visible accumulations of fluid within or beneath the epithelium, >0.5cm in diameter
Cyst	Closed cavity or sac (normal or abnormal) with an epithelial, endothelial or membranous lining and containing fluid or semisolid material
Ecchymosis	Macular area of haemorrhage >2cm in diameter (bruise)
Erosion	Loss of epithelium which usually heals without scarring; it commonly follows a blister
Erythema	Redness of the mucosa produced by atrophy, inflammation, vascular congestion or increased perfusion
Exfoliation	The splitting off of the epithelial keratin in scales or sheets
Fibrosis	The formation of excessive fibrous tissue
Fissure	Any linear gap or slit in the skin or mucosa
Gangrene	Death of tissue, usually due to loss of blood supply
Haematoma	A localized tumour-like collection of blood
Keloid	A tough heaped-up scar that rises above the rest of the skin, is irregularly shaped and tends to enlarge progressively
Macule	A circumscribed alteration in colour or texture of the mucosa
Nodule	A solid mass in the mucosa or skin which can be observed as an elevation or can be palpated; it is >0.5cm in diameter
Papule	A circumscribed palpable elevation <0.5cm in diameter
Petechia (pl. petechiae)	A punctate haemorrhagic spot approximately 1–2mm in diameter
Plaque	An elevated area of mucosa >0.5cm in diameter
Pustule	A visible accumulation of free pus
Scar	Replacement by fibrous tissue of another tissue that has been destroyed by injury or disease. An <i>atrophic</i> scar is thin and wrinkled. A <i>hypertrophic</i> scar is elevated; with excessive growth of fibrous tissue. A <i>cribriform</i> scar is perforated with multiple small pits
Sclerosis	Diffuse or circumscribed induration of the submucosal and/or subcutaneous tissues
Tumour	Literally a swelling. The term is used to imply enlargement of the tissues by normal or pathological material or cells that form a mass. The term should be used with care, as many patients believe it implies a malignancy with a poor prognosis
Ulcer	A loss of epithelium, often with loss of the underlying tissues, produced by sloughing of necrotic tissue
Vegetation	A growth of pathological tissue consisting of multiple closely set papillary masses
Vesicle	Small (<0.5cm in diameter) visible accumulation of fluid within or beneath the epithelium
Wheal	A transient area of mucosal or skin oedema, white, compressible and usually evanescent

- The supraclavicular region should be examined at the same time as the rest of the neck; lymph nodes here may extend up into the posterior triangle of the neck on the scalene muscles, behind the sternomastoid.
- Parapharyngeal and tracheal lymph nodes can be compressed lightly against the trachea.
- Some information can be gained by the texture and nature of the lymphadenopathy.
- Tenderness and swelling should be documented. Lymph nodes that are tender may be inflammatory (lymphadenitis). Consistency should be noted. Nodes that are increasing in size and are hard, or fixed to adjacent tissues may be malignant.

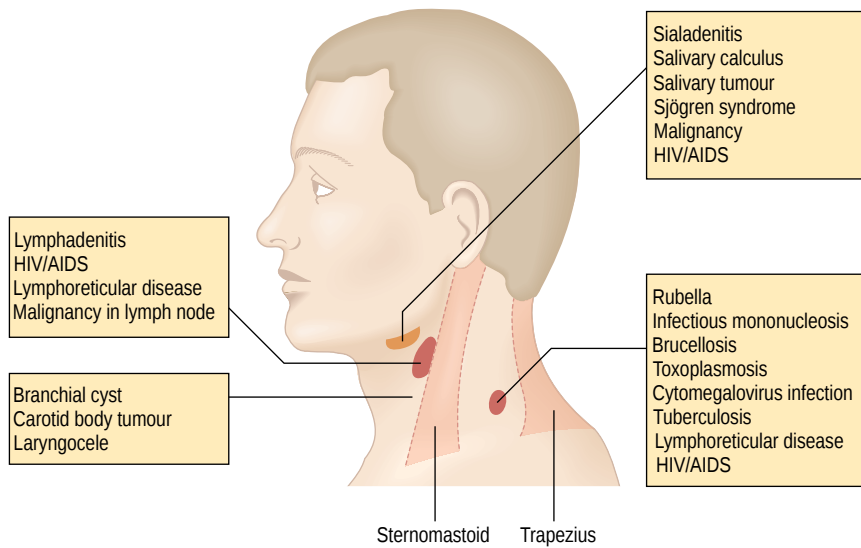


Fig. 2.8 Some causes of neck swelling

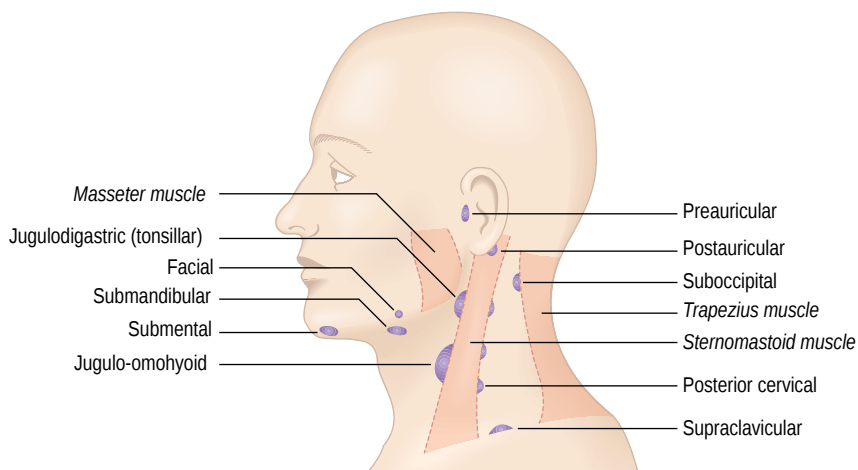


Fig. 2.9 Cervical lymph nodes

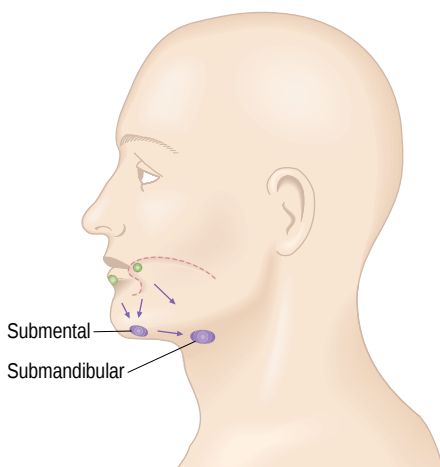


Fig. 2.10 Submental and submandibular lymph nodes

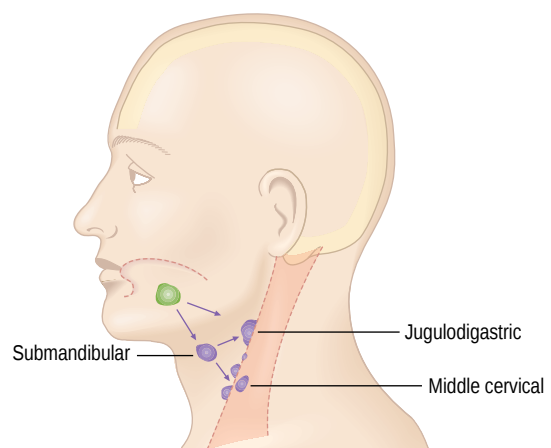


Fig. 2.11 Submandibular and deep cervical lymph nodes

► Box 2.2

The cervical lymph nodes and their main drainage areas

Area	Draining lymph nodes
Scalp, temporal region	Superficial parotid (pre-auricular)
Scalp, posterior region	Occipital
Scalp, parietal region	Mastoid
Ear, external	Superficial cervical over upper part of sternomastoid muscle
Ear, middle	Parotid
Over angle of mandible	Superficial cervical over upper part of sternomastoid muscle
Medial part of frontal region, medial eyelids, skin of nose	Submandibular
Lateral part of frontal region, lateral part of eyelids	Parotid
Cheek	Submandibular
Upper lip	Submandibular
Lower lip	Submental
Lower lip, lateral part	Submandibular
Mandibular gingivae	Submandibular
Maxillary teeth	Deep cervical
Maxillary gingivae	Deep cervical
Tongue tip	Submental
Tongue, anterior two-thirds	Submandibular, some midline cross-over of lymphatic drainage
Tongue, posterior third	Deep cervical
Tongue ventrum	Deep cervical
Floor of mouth	Submandibular
Palate, hard	Deep cervical
Palate, soft	Retropharyngeal and deep cervical
Tonsil	Jugulodigastric

- Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility. Generalized lymphadenopathy with or without enlargement of other lymphoid tissue, such as liver and spleen (hepatosplenomegaly), suggests a systemic cause.

The temporomandibular joints (TMJ) and muscles of mastication should be examined and palpated. Although disorders that affect the TMJ often appear to be unilateral, the joint should not be viewed in isolation, but always considered along with its opposite joint, as part of the stomatognathic system. Some practitioners palpate using a pressure algometer to standardize the force used, and undertake range-of-movement (ROM) measurements. The area should be examined by inspecting:

- Facial symmetry, for evidence of enlarged masseter muscles (masseteric hypertrophy) suggestive of clenching or bruxism. A bruxchecker can help confirm bruxism.
- Mandibular opening and closing paths, noting any noises or deviations.
- Mandibular opening extent, measuring the inter-incisal distance at maximum mouth opening.
- Lateral excursions, measuring the amount achievable.
- Joint noises, by listening (a stethoscope placed over the joint can help).
- Both condyles, by palpating them, via the external auditory meatus, to detect tenderness posteriorly, and by using a single finger placed over the joints in front of the ears, to detect pain, abnormal movements or clicking within the joint.

- Masticatory muscles on both sides, noting tenderness or hypertrophy:
 - Masseters, by intraoral–extraoral compression between finger and thumb. Palpate the masseter bimanually by placing a finger of one hand intraorally and the index and middle fingers of the other hand on the cheek over the masseter over the lower mandibular ramus.
 - Temporalis, by direct palpation of the temporal region and by asking the patient to clench the teeth. Palpate the insertion of the temporalis tendon intraorally along the anterior border of the ascending mandibular ramus.
 - Lateral pterygoid (lower head), by placing a little finger up behind the maxillary tuberosity (tenderness is the ‘pterygoid sign’). Examine it indirectly by asking the patient to open the jaw against resistance and to move the jaw to one side while applying a gentle resistance force.
 - Medial pterygoid muscle, intraorally lingually to the mandibular ramus.
- The dentition and occlusion. This may require monitoring of study models on a semi or fully adjustable articulator. Note particularly missing premolars or molars, and attrition.
- The mucosa. Note particularly occlusal lines and scalloping of the tongue margins, which may indicate bruxism and tongue pressure.

Examine the jaws. There is a wide normal individual variation in morphology of the face. Most individuals have facial asymmetry but of a degree that cannot be regarded as abnormal. Maxillary, mandibular or zygomatic deformities or lumps may be more reliably confirmed by inspection from above (maxillae/zygomas) or behind (mandible). The jaws should be palpated to detect swelling or tenderness. Maxillary air sinuses can be examined by palpation for tenderness over the maxillary antrum, which may indicate sinus infection. Transillumination or endoscopy can be helpful. The major salivary glands should be inspected and palpated (parotids and submandibulars) for:

- symmetry
- evidence of enlarged glands
- evidence of salivary flow from salivary ducts
- evidence of salivary pooling in the floor of mouth
- saliva appearance
- evidence of oral dryness (food residues; lipstick on teeth; scarce saliva; mirror sticks to mucosa); sialometry (salivary flow rate; see page 31).

Salivary glands are palpated in the following way:

- Parotid glands are palpated by using fingers placed over the glands in front of the ears, to detect pain or swelling. Early enlargement of the parotid gland is characterized by outward deflection of the lower

part of the ear lobe, which is best observed by looking at the patient from behind. This sign may allow distinction from simple obesity. Swelling of the parotid sometimes causes trismus. Swellings may affect the whole or part of a gland, or tenderness may be elicited. The parotid duct (Stensen’s duct) is most readily palpated with the jaws clenched firmly, since it runs horizontally across the upper masseter where it can be gently rolled; the duct opens at a papilla on the buccal mucosa opposite the upper molars.

- Submandibular glands are palpated bimanually between fingers inside the mouth and extraorally. The submandibular gland is best palpated bimanually with a finger of one hand in the floor of the mouth lingual to the lower molar teeth, and a finger of the other hand placed over the submandibular triangle. The submandibular duct (Wharton’s duct) runs anteromedially across the floor of the mouth to open at the side of the lingual fraenum.

Examine the cranial nerves (Table 2.1). In particular, facial movement should be tested and facial sensation determined. Facial symmetry is best seen as the patient is talking. Movement of the mouth as the patient speaks is important, especially when they allow themselves the luxury of some emotional expression. The upper part of the face is bilaterally innervated and thus loss of wrinkles on one-half of the forehead or absence of blinking suggests a lesion in the lower motor neurone. Examination of the upper face (around the eyes and forehead) is carried out in the following way:

- If the patient is asked to close their eyes the palsy may become obvious, with the affected eyelid failing to close and the globe turning up so that only the white of the eye is showing (Bell’s sign).
- Weakness of orbicularis oculi muscles with sufficient strength to close the eye can be compared with the normal side by asking the patient to close the eyes tight and observing the degree of force required to part the eyelids.
- If the patient is asked to wrinkle the forehead, weakness can be detected by the difference between the two sides.

The lower face (around the mouth) is best examined by asking the patient to:

- smile
- bare the teeth or purse the lips
- blow out the cheeks or whistle.

The cranial nerves can be examined further:

- The corneal reflex: this depends on the integrity of the trigeminal and facial nerves, either of which if defective will give a negative response. It is important to

Table 2.1
Examination of cranial nerves

Cranial nerve		Findings in lesions
I	Olfactory	Impaired sense of smell for common odours (do not use ammonia)
II	Optic	Visual acuity reduced using Snellen types $\pm$ ophthalmoscopy: nystagmus Visual fields by confrontation impaired Pupil responses may be impaired
III	Oculomotor	Diplopia; strabismus; eye looks down and laterally ('down and out') Eye movements impaired Ptosis (drooping eyelid) Pupil dilated Pupil reactions: direct reflex impaired, but consensual reflex intact
IV	Trochlear	Diplopia, particularly on looking down Strabismus (squint) No ptosis Pupil normal and normal reactivity
V	Trigeminal	Reduced sensation over face $\pm$ corneal reflex impaired $\pm$ taste sensation impaired Motor power of masticatory muscles reduced, with weakness on opening jaw; jaw jerk impaired Muscle wasting
VI	Abducens	Diplopia (double vision) Strabismus Lateral eye movements impaired to affected side
VII	Facial	Impaired motor power of facial muscles on smiling, blowing out cheeks, showing teeth, etc. Corneal reflex reduced $\pm$ taste sensation impaired
VIII	Vestibulocochlear	Impaired hearing (tuning fork at 256 Hz) Impaired balance $\pm$ nystagmus $\pm$ tinnitus
IX	Glossopharyngeal	Reduced gag reflex Deviation of uvula Reduced taste sensation Voice may have nasal tone
X	Vagus	Reduced gag reflex Voice may be impaired
XI	Accessory	Motor power of trapezius and sternomastoid reduced
XII	Hypoglossal	Motor power of tongue impaired, with abnormal speech $\pm$ fasciculation, wasting, ipsilateral deviation on protrusion

test facial light touch sensation in all areas but particularly the corneal reflex. Lesions involving the ophthalmic division cause corneal anaesthesia, which is tested by gently touching the cornea with a wisp of cotton wool twisted to a point. Normally, this procedure causes a blink but, if the cornea is anaesthetic (or if there is facial palsy), no blink follows, provided that the patient does not actually see the cotton wool. If the patient complains of complete facial or hemifacial anaesthesia, but the corneal reflex is retained or there is apparent anaesthesia over the angle of the mandible (an area not innervated by the trigeminal nerve), then the symptoms are probably functional (non-organic).

- Taste: unilateral loss of taste associated with facial palsy indicates that the facial nerve is damaged proximal to the chorda tympani nerve.
- Hearing: hyperacusis may be caused by paralysis of the stapedius muscle and this suggests the facial nerve lesion is proximal to the nerve to the stapedius.
- Lacrimation: this is tested by hooking a strip of Schirmer or litmus paper in the lower conjunctival fornix. The strip should dampen to at least 15mm in 1 minute if tear production is normal. The contralateral eye serves as a control (Schirmer's test). Secretion is diminished in proximal lesions of the facial nerve, such as those involving the geniculate ganglion or in the internal auditory meatus, or in disorders of exocrine glands, such as Sjögren syndrome.

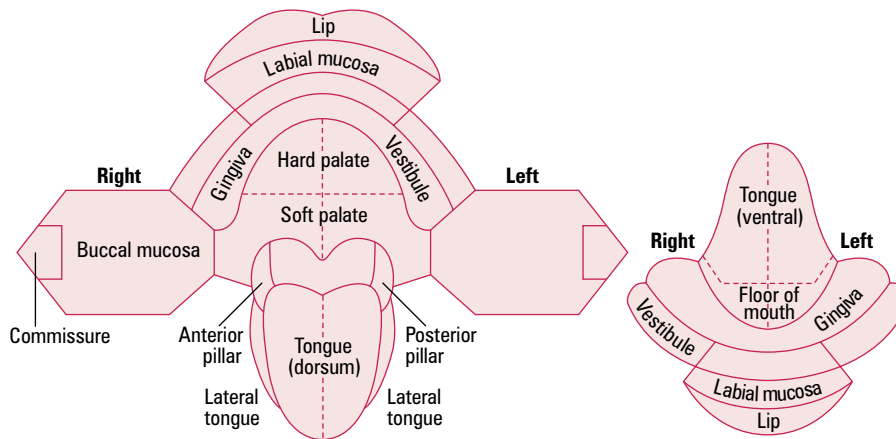


Fig. 2.12 Mouth chart

- Facial sensation: progressive lesions affecting the sensory part of the trigeminal nerve initially result in a diminishing response to light touch (cotton wool) and pin-prick (gently pricking the skin with a sterile pin or needle without drawing blood), and later there is complete anaesthesia.

Intraoral examination

Few oral diseases are life threatening, though cancer and pemphigus are obvious exceptions. Most diseases have a local cause and can be recognized fairly readily. Even those that are life threatening, such as oral cancer in particular, can be detected at an exceedingly early stage. However, even now, oral cancer is sometimes overlooked at examination, and the delay between the onset of symptoms of oral cancer and the institution of definitive treatment still often exceeds 6 months. The same applies to pemphigus.

Many systemic diseases, particularly infections and diseases of the blood, gastrointestinal tract and skin, also cause oral signs or symptoms that may constitute the main complaint, particularly, for example, in some patients with HIV, leukopenia or leukaemia.

The examination, therefore, should be conducted in a systematic fashion to ensure that all areas are included. If the patient wears any removable prostheses or appliances, these should be removed in the first instance, although it may be necessary later to replace the appliance to assess its fit, function and relationship to any lesion.

Complete visualization with a good source of light is essential. All mucosal surfaces should be examined, starting away from the location of any known lesions or the focus of complaint, and lesions recorded on a diagram (Fig. 2.12). The lips should first be inspected. The labial mucosa, buccal mucosa, floor of the mouth and

ventrum of the tongue, dorsal surface of the tongue, hard and soft palates, gingivae and teeth should then be examined in sequence (Box 2.3):

- Lips: features, such as cyanosis, are seen mainly in the lips in cardiac or respiratory disease; angular cheilitis is seen mainly in oral candidiasis or iron or vitamin deficiencies. Many adults have a few yellowish pinhead-sized papules in the vermillion border (particularly of the upper lip) and at the commissures; these are usually ectopic sebaceous glands (Fordyce spots), and may be numerous, especially as age advances.
- Labial mucosa normally appears moist with a fairly prominent vascular arcade. Examination is facilitated if the mouth is gently closed at this stage, so that the lips can then be everted to examine the mucosa. In the lower lip, the many minor salivary glands, which are often exuding mucus, are easily visible. The lips, therefore, feel slightly nodular and the labial arteries are readily felt.
- Cheek (buccal) mucosa is readily inspected if the mouth is held half open. The vascular pattern and minor salivary glands so prominent in the labial mucosa are not obvious in the buccal mucosa, but Fordyce spots may be conspicuous, particularly near the commissures and retromolar regions in adults and there may be a faint horizontal white line where the teeth meet (linea alba). Place the surface of a dental mirror against the buccal mucosa. The mirror should slide and lift off easily; if it adheres to the mucosa, then xerostomia is present.
- The floor of the mouth and the ventrum of the tongue are best examined by asking the patient to push the tongue first into the palate and then into each cheek in turn. This raises for inspection the floor of the mouth – an area where tumours may start (the coffin or graveyard area of the mouth). Its posterior part is the most difficult area to examine well and one where lesions are most easily missed. Lingual veins are prominent and,

► Box 2.3

The more commonly used tooth notations

Palmer

Permanent dentition

Upper

87654321 | 12345678

Right

Left

87654321 | 12345678

Lower

Deciduous dentition (anonymous classification)

EDCBA | ABCDE

EDCBA | ABCDE

Haderup

Permanent dentition

(8+)(7+)(6+)(5+)(4+)(3+)(2+)(1+) | (+1)(+2)(+3)(+4)(+5)(+6)(+7)(+8)

(8-)(7-)(6-)(5-)(4-)(3-)(2-)(1-) | (-1)(-2)(-3)(-4)(-5)(-6)(-7)(-8)

Deciduous dentition

(50+)(40+)(30+)(20+)(10+) | (+01)(+02)(+03)(+04)(+05)

(50-)(40-)(30-)(20-)(10-) | (-01)(-02)(-03)(-04)(-05)

Universal

Permanent dentition

1 2 3 4 5 6 7 8 | 9 10 11 12 13 14 15 16
32 31 30 29 28 27 26 25 | 24 23 22 21 20 19 18 17

Deciduous dentition

A B C D E | F G H I J
T S R Q P | O N M L K

Fédération Dentaire Internationale (two-digit)

Permanent dentition

18 17 16 15 14 13 12 11 | 21 22 23 24 25 26 27 28
48 47 46 45 44 43 42 41 | 31 32 33 34 35 36 37 38

Deciduous dentition

55 54 53 52 51 | 61 62 63 64 65
85 84 83 82 81 | 71 72 73 74 75

in the elderly, may be conspicuous (lingual varices). Bony lumps on the alveolar ridge lingual to the premolars are most often tori (torus mandibularis) – a normal variant. During this part of the examination the quantity and consistency of saliva should be assessed. Examine for the pooling of saliva in the floor of the mouth; normally there is a pool of saliva.

- The dorsum of the tongue is best inspected by protrusion, when it can be held with gauze. The anterior two-thirds is embryologically and anatomically distinct from the posterior third, and separated by a dozen or so large circumvallate papillae. The anterior two-thirds is coated with many filiform, but relatively few fungiform papillae. Behind the circumvallate papillae, the tongue contains several large lymphoid masses (lingual tonsil) and the foliate papillae lie on

the lateral borders posteriorly. These are often mistaken for tumours. The tongue may be fissured (scrotal), but this is a developmental anomaly. A healthy child's tongue is rarely coated, but a mild coating is not uncommon in healthy adults. The voluntary tongue movements and sense of taste should be formally tested. Abnormalities of tongue movement (neurological or muscular disease) may be obvious from dysarthria (abnormal speech) or involuntary movements, and any fibrillation or wasting should be noted. Hypoglossal palsy may lead to deviation of the tongue towards the affected side on protrusion. Formal taste testing with salt, sweet, sour and bitter should be carried out by applying solutions of salt, sugar, dilute acetic acid and 5% citric acid to the tongue on a cotton swab or cotton bud.

- The palate and fauces consist of an anterior hard palate and posterior soft palate, and the tonsillar area and oropharynx. The mucosa of the hard palate is firmly bound down as a mucoperiosteum (similar to the gingivae) and with no obvious vascular arcades. Ridges (rugae) are present anteriorly on either side of the incisive papilla that overlies the incisive foramen. Bony lumps in the posterior centre of the vault of the hard palate are usually tori (torus palatinus). Patients may complain of a lump distal to the upper molars that they think is an unerupted tooth, but the pterygoid hamulus or tuberosity is usually responsible for this complaint. The soft palate and fauces may show a faint vascular arcade. Just posterior to the junction with the hard palate is a conglomeration of minor salivary glands. This region is often also yellowish. The palate should be inspected and movements examined when the patient says 'Aah'. Using a mirror, this also permits inspection of the posterior tongue, tonsils, oropharynx, and can even offer a glimpse of the larynx. Glossopharyngeal palsy may lead to uvula deviation to the contralateral side. Bifid uvula may signify a submucous cleft palate.
- Gingivae in health are firm, pale pink, with a stippled surface, and have sharp gingival papillae reaching up between the adjacent teeth to the tooth contact point. Look for gingival redness, swelling, or bleeding on gently probing the gingival margin. The 'keratinized' attached gingivae (pale pink) is normally clearly demarcated from the non-keratinized alveolar mucosa (vascular) that runs into the vestibule or sulcus. Bands of tissue, which may contain muscle attachments, run centrally from the labial mucosa onto the alveolar mucosa and from the buccal mucosa in the premolar region onto the alveolar mucosa (fraenae).
- Teeth: the dentition should be checked to make sure that the expected complement of teeth is present for the patient's age. Extra teeth (supernumerary teeth) or deficiency of teeth, partial loss (hypodontia; oligodontia) or complete loss (anodontia) can be features of many syndromes, but teeth are far more frequently

missing because they are unerupted, impacted or lost as a result of caries or periodontal disease. The teeth should be fully examined for signs of disease, either malformations, such as hypoplasia or abnormal colour, or acquired disorders such as dental caries, staining, erosion or abrasion or fractures. The laser fluorescence device DIAGNOdent may help caries detection. Apex locators, such as Propex (third generation) and Raypex-4 (fourth generation), may help define root fractures. The occlusion of the teeth should also be checked; it may show attrition or may be disturbed, as in some jaw fractures or dislocation of the mandibular condyles.

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3

Diagnosis: investigations

Accurate diagnosis is the only true cornerstone on which rational treatment can be built.

C Noyek

Investigations

Following history taking and examination, investigations may be required to help make or confirm the diagnosis and prognosis, or sometimes simply to exclude some diagnoses in order to reassure the patient (and partner, family or clinician). Inadequate investigation could lead to a:

- misdiagnosis
- missed diagnosis
- complaint of bad practice
- legal action.

However, superfluous investigations may be:

- liable to engender undue anxiety on the part of the patient, partner or relatives
- time consuming
- expensive
- occasionally associated with adverse effects, or even dangerous.

The following points should be borne in mind with regard to any form of investigation:

- The first principle must be to do no harm.
- Informed consent is required.
- Only an operator adequately skilled in a procedure should perform it.
- Surgical procedures are invasive and this includes venepuncture and biopsy; an oral biopsy is rarely a pleasant procedure.

This chapter discusses a number of common investigations: other appear elsewhere in the book.

Informed consent

It is the duty of dental staff to ensure they try and help patients understand their condition. Patients commonly complain that they have been ill-informed about their diagnosis, investigations and the results of these. Patients

should always be involved in the decision-making about their management. Careful discussion with the patient is the best approach. Other ways to help are by:

- Writing important points down for the patient.
- Using patient information sheets, examples of which are included in this book.
- Offering guidance to other sources of information, such as written material and the internet.
- Arranging contact with other patients with the same problems, either individually or through a patient self-help group. Patients with serious conditions, such as cancer, pemphigus, trigeminal neuralgia, Behçet's syndrome or Sjögren syndrome, particularly may benefit from this.
- Explaining the condition, diagnosis, investigations, management and prognosis to someone who can act as an advocate. This could be the patient's parent, partner, friend or relative. This should only be done if appropriate and only with the patient's express consent.

Consent is implied for taking a history and performing relevant clinical examinations. However, investigations are another matter; the dentist must clearly explain the:

- nature
- potential benefit
- possible adverse effects
- problems and advantages of not carrying out the investigations.

These points must be explained clearly to the patient, in a way that can be readily understood. Routine urinalysis, for example, is usually accepted as part of medical and insurance examinations though some patients question its use in dentistry. For other procedures, informed consent should always first be obtained. This applies particularly where there are sensitive issues, such as HIV infection, when the patient must be professionally counselled before serotesting is performed. It is also important where there could be adverse effects, such as pain, bleeding, infection, scarring or loss of sensation after a biopsy.

Verbal informed consent is adequate for non-invasive procedures, but for invasive or risky procedures a signed, witnessed and written informed consent should be obtained. Remember that patients are free to decline any or all investigations should they so wish, but it is wise for the clinician to clearly record that decision in writing in the case records.

'A patient has the right under common law to give or withhold consent to medical examination of treatment. This is one of the basic principles of healthcare. Patients are entitled to receive sufficient information in a way they can understand about the proposed treatments, the possible alternatives and any substantial risk or risks which may be special in kind or magnitude or special to the patient, so that they can make a balanced judgement.'

(UK Health Department 19.2.99. HSC 1999/031).

All body fluids and tissues are potentially infectious. Barrier precautions must, therefore, always be employed in order to prevent transmission of infection to patients or staff during investigations involving body fluids or tissues.

These procedures can often be carried out in general practice but, for a number of reasons, the dental professional may elect to refer to a specialist. The same applies to other investigations, particularly where there are sensitive issues such as possible HIV infection, when medical experience or a medical or specialist opinion could be helpful if not essential.

Urinalysis

This is routinely performed with 'dip-sticks'. It may reveal:

- glycosuria, which may suggest diabetes mellitus
- ketonuria, which may be a sign of diabetic ketoacidosis or starvation
- bilirubin or urobilinogen, which may indicate hepato-biliary disorders
- proteinuria, which may be due to menstruation, or indicate renal, urinary tract or cardiac disease
- haematuria, which may be due to menstruation, or indicate renal or urinary tract disease.

Blood testing

Details of the various blood tests commonly used are shown in [Table 3.1](#). During venepuncture, remember:

- The antecubital fossa is most commonly used since veins are usually large and easily seen. Veins at other sites, such as the dorsum of hand or the cephalic vein, can be difficult to identify and venepuncture can be painful there.
- Blood is withdrawn automatically into a vacutainer. If a syringe is used, withdraw slowly, making sure that there is no air in the syringe. Too rapid removal of blood may cause haemolysis.
- If the specimen tube contains anticoagulant, ensure mixing by gently rolling the tube.

- Carefully dispose of the needle in the sharps container.
- Label the blood collection tubes with the patient's name, number, date and time, etc.
- Complete and sign the appropriate request forms and give relevant clinical data, patient's name and number, etc.

Skin testing

Absorption of many substances through the intact skin is poor and variable, but direct application to the surface of the skin is used for patch testing. The epidermal barrier may be overcome either by removing it or by introducing the material directly with a needle into the dermis. The following techniques for skin testing are most commonly used.

Epicutaneous tests – patch tests. Patch tests are usually carried out on the forearm and are used to detect contact allergy of the delayed hypersensitivity type. They are usually read at 48–72 hours and again up to 1 week, but can also be read at 0.5 hours to detect contact urticaria. At times patch testing may usefully be combined with scratch testing (see below).

Intradermal injection. The back, and the flexor aspects of the forearms are most conveniently used. A test solution must always be compared with a control solution (e.g. sterile saline) injected in a comparable site at the same time. A positive test may be taken as one which is significantly different from the control. Assessment of what is significant is difficult and varies with the enthusiasm of the tester. Resuscitation equipment and 1 in 1000 epinephrine (adrenaline) must be at hand to cope with any untoward allergic reactions. The test injection is made into the superficial layer of the dermis through a fine-bore (26G or 27G) needle with its bevel pointing upwards. The quantity of which may be conveniently injected varies from 0.01 to 0.1 ml. Precise measurement of smaller quantities is difficult and requires syringes with especially well-fitting plungers and a micrometer screw gauge. For routine clinical purposes an approximation is sufficient, either 0.05ml or the amount, which just causes a visible wheal (0.01–0.02ml).

The optimal time for reading the reaction varies with the pharmacological agent or the type of immunological reaction. Most such tests are read at either 15–20 minutes or at 48 hours, but it may be important to read the tests at other times, e.g. at 4–12 hours or after 4 days.

Prick test. This is a modification of the intradermal injection. A small quantity of the test solution is placed on the skin and a prick made through it with a sharp needle. This should be superficial and not sufficient to draw blood. The size of the wheal and flare are measured after 15 minutes. This test gives reproducible results and is convenient for much routine

Table 3.1
Blood tests

Test	Blood sample required	Comments
<i>Full blood count (FBC)</i>	5ml anticoagulated with dry potassium edetate (EDTA) and received in the haematology laboratory within 24 hours	One of the laboratory investigations most frequently requested because anaemia and changes in the white blood cell count occur so commonly in a wide variety of diseases. Blood cells are usually counted and sized in automatic blood cell counters. Folate can be assayed on this sample. Blood film is prepared from the same sample if indicated by the history or by the blood count results, for visual inspection of blood cells.
<i>Erythrocyte sedimentation rate (ESR)</i>		Global rate (ESR) or plasma measurements of non-specific plasma protein changes in viscosity ('plasma viscosity'): principally, increases in the concentration of certain globulins, and a fall in the albumin level. The ESR also increases with anaemia.
<i>Coagulation screen</i>	5ml anticoagulated with liquid sodium citrate and received in the haematology laboratory within 4 hours [or within 24 hours for warfarin control by the prothrombin time or International Normalized Ratio (INR)]	Required to diagnose coagulation disorders
<i>Ferritin, iron, transferrin, folate and vitamin B₁₂ (cobalamin) levels</i>	10ml added to a plain tube, and received in the haematology laboratory within 24 hours.	Useful in the diagnosis of anaemias due to deficiencies
<i>Blood grouping and cross-matching</i>	10ml added to a plain tube, and received in the haematology laboratory within 4 hours	Required prior to blood cell transfusion or major surgery
<i>Blood glucose</i>	Special tube (sodium fluoride)	Used to diagnose hypoglycaemia or hyperglycaemia, which is often due to diabetes mellitus
<i>Serum urea, creatinine and electrolyte levels</i>	Plain tube (no anticoagulant)	Used to diagnose renal failure (raised urea and creatinine levels) and electrolyte disturbance
<i>Serum liver function tests include bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, albumin and globulin</i>		Useful in the diagnosis of jaundice, liver and biliary tract disorders
<i>Serum calcium, phosphate and alkaline phosphatase</i>		Useful in the diagnosis of metabolic bone disease in particular
<i>Serology</i>		Useful for assay of various antibodies

allergy testing. Because of the discrepancy in quantities injected, the testing solutions are made up at different strengths for prick testing and intradermal testing. The intradermal injections of prick test solutions may be dangerous.

Modified prick test. Here a drop of the test solution is placed on the skin. A needle is then inserted very superficially and almost horizontally into the skin and lifted to

raise a tiny tent of epidermis. This test is slightly more sensitive than the ordinary prick test, but gives no more reproducible results.

Scratch test. The scratch test resembles the prick test. A linear scratch about 1cm long, but not sufficient to draw blood, is made through the epidermis. This test gives less reproducible results than the prick test.

Table 3.2
Main indications for biopsy

Indication	Examples
Lesions which have neoplastic or premalignant features or are enlarging	Erythroplakia Leukoplakia Lichen planus Focal pigmented lesions Lumps
Persistent lesions of uncertain aetiology	Soft or hard tissue
Persistent lesions failing to respond to treatment	Ulcers or lesions, such as some radiolucent or radio-opaque bone lesions
Persistent focal lesions involving the gingival/periodontium	Lumps, ulcers or non-healing extraction sockets
Confirmation of clinical diagnosis	Labial salivary gland biopsy to confirm Sjögren syndrome
Lesions causing the patient extreme concern	Patients may prefer the biopsy or excision biopsy of a persistent red, white or pigmented lesion or lump

Biopsy

Biopsy is the removal of a small piece of tissue from the living body for the purpose of diagnosis by microscopic examination. It is often indicated in order to confirm or make a precise diagnosis, especially in the case of mucosal lesions, when a specimen for immunostaining is often also called for.

Indications for biopsy include (Table 3.2):

- lesions that have neoplastic or premalignant features or are enlarging
- persistent lesions that are of uncertain aetiology
- persistent lesions that are failing to respond to treatment
- confirmation of the clinical diagnosis
- lesions that are causing the patient extreme concern.

Biopsy technique

Tissue may be obtained by two main methods: techniques not requiring anaesthesia (e.g. exfoliative cytology and brush biopsy) and techniques requiring local anaesthesia. Those requiring local anaesthesia include:

- scalpel or tissue punch – incisional biopsy
- scalpel or laser cutting – excisional biopsy
- curettage
- needle biopsy, these include:
 - cutting biopsy using a 14G Tru-Cut needle, which is wide bore
 - cutting biopsy using a 16G Vim Silverman needle
 - fine-needle cutting biopsy (FNCB) using an 18G TSK Surecut needle

- fine-needle aspiration biopsy (FNA or FNAB) or cytology (FNAC) using a 22G or 25G standard disposable needle, sometimes as ultrasound-guided fine-needle aspiration cytology (US-FNAC).

Figures 3.1–3.3 show equipment required. In the case of suspected potentially malignant or malignant mucosal lesions it can be difficult to decide exactly which is the part of the lesion that is best biopsied. Most significant information can be gained from red mucosal areas (erythroplasia) rather than white areas (leukoplakia) and it can sometimes be helpful to stain the mucosa before biopsy with toluidine blue dye (vital staining), which is taken up by nuclei and stains pathological areas mainly, causing suspect mucosal areas to stain blue. The technique is of limited value in a primary-care setting, but may have a place in the hands of an experienced clinician, in high-risk patients. The usual procedure is as follows: the patient is asked to rinse for 20 seconds with a solution of 1% acetic acid to cleanse the area of mucus, etc.; they then rinse for 20 seconds with plain water; they then rinse for 60 seconds with 1% aqueous toluidine blue solution; they then rinse for 20 seconds with a 1% solution of acetic acid; and, finally, they rinse for 20 seconds with water.

Usually a single biopsy is taken, but multiple biopsies may be indicated where:

- additional investigations, such as immunostaining, are required
- malignant disease is suspected
- there are widespread leukoplakic or erythroplakic field changes (such biopsies may be termed ‘geographic’ biopsies).

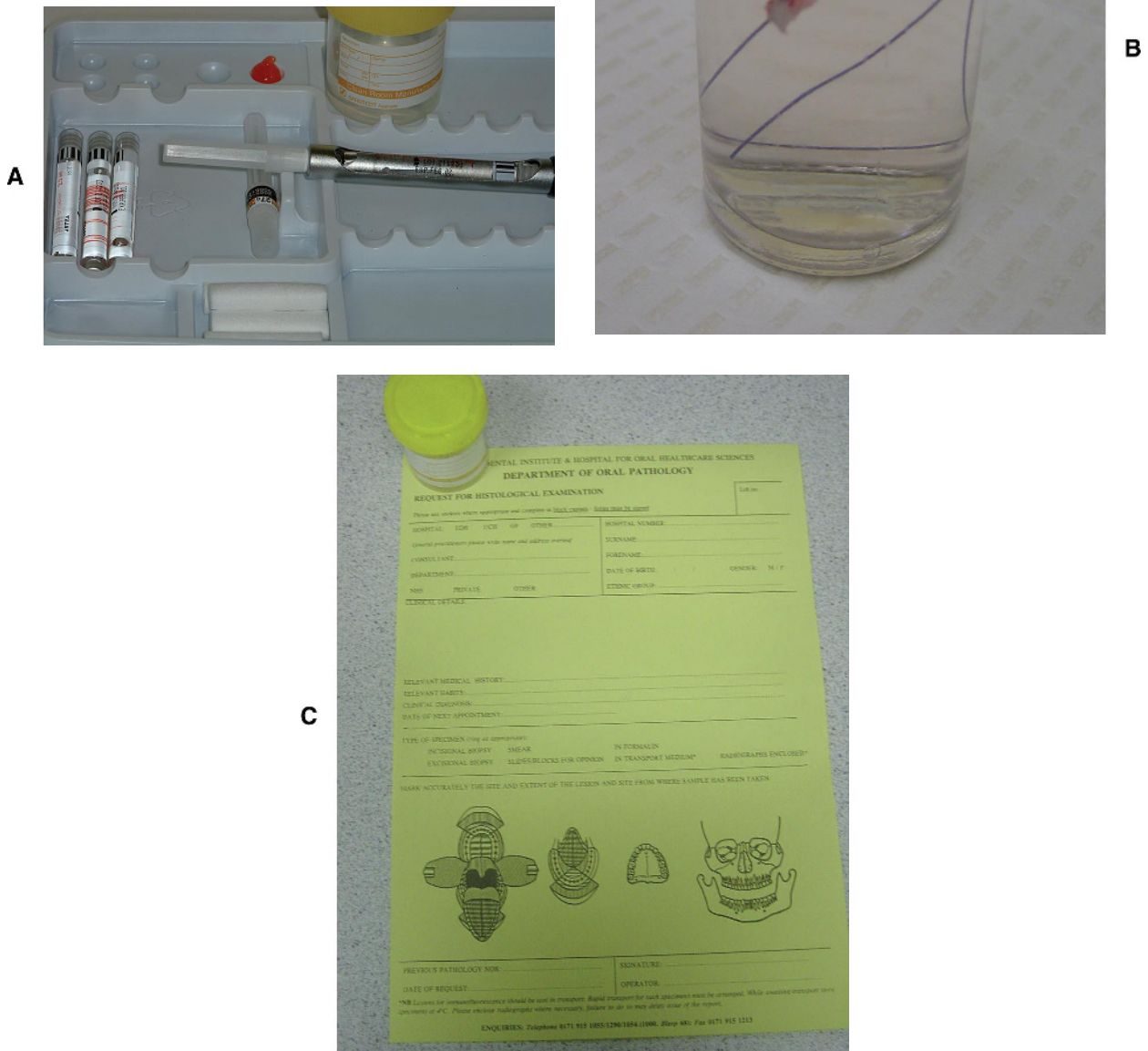


Fig. 3.1 (a) Biopsy tray, (b) pot and (c) form

Biopsy procedure

Informed consent is mandatory for biopsy as for all operative procedures, particularly noting any possible adverse effects, such as postoperative pain, bleeding or loss of sensation. Care must be taken not to produce anxiety where it is not necessary; some patients equate

biopsy with a diagnosis of cancer. Complete the request form with the:

- patient's full name
- patient's date of birth
- hospital number, if applicable
- date

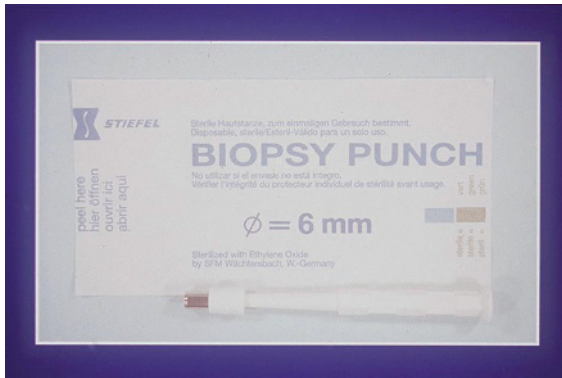


Fig. 3.2 Biopsy punch

Patient information sheet

POST-BIOPSY CARE

- A biopsy is the taking of a small piece of tissue for microscopic examination.
- This is carried out usually after a local anaesthetic injection in the area, such as used for fillings.
- Biopsy is painless, though a little sore when the injection wears off after a couple of hours.
- Stitches may or may not be used.
- Stitches may be resorbable or need to be removed in the next week. It is usually not a problem if the stitches come out earlier than 1 week.
- Any interventional procedure may occasionally result in complications, such as a little:
 - bleeding: pressure for 5–10 minutes from a gauze swab will almost invariably stop the bleeding
 - soreness or pain: paracetamol/acetaminophen will usually control any discomfort; aspirin should not be used as it can cause bleeding
 - swelling: this should subside spontaneously over 3–4 days
 - bruising: this should clear spontaneously over 4–5 days.
- Rarely there may be:
 - altered sensation
 - restricted mouth opening
 - reactions to drugs
 - allergies
 - infection.
- If you are at all concerned, for advice kindly telephone.....
- However, there are usually no long-term consequences. The scar is usually almost invisible, any discomfort goes quickly and any slight numbness recovers.

- site of biopsy
- clinical résumé
- dates, and numbers, of all previous biopsies.

The container must be labelled clearly with:

- patient's full name
- patient's date of birth



Fig. 3.3 Biopsy instruments

- number
- date
- specimen site.

Mucosal biopsies

Mucosal biopsies are *excisional* (removal of the complete lesion) or *incisional* and taken with a scalpel or biopsy punch, or sometimes a diathermy or laser, usually under local analgesia. Excisional biopsy is preferred for small, isolated and probably benign lesions.

The biopsy should include lesional and normal tissue and should be large enough to handle, and to provide adequate information about the lesion. In the case of ulcerated mucosal lesions, most histopathological information is gleaned from the perilesional tissue, since by definition most epithelium is lost from the ulcer itself. The punch has the advantages for incision biopsy that:

- the incision is controlled
- an adequate specimen is obtained (typically 4mm or 6mm in diameter)
- the patient is not disturbed by the sight of a scalpel
- suturing may not be required.

However, only a fairly small biopsy is obtained with the punch and, in some instances, epithelium may be sheared off. If a larger piece of tissue is needed, or the whole lesion is to be removed, the scalpel has advantages, particularly when the lesion is on the gingivae, especially lingually or other areas in which it is difficult to gain access with a punch or when mucosa is fragile (e.g. pemphigus). A number 15 blade is usually chosen.

To carry out a biopsy:

- a local analgesic should be given
- ensure tissue representative of the lesion is obtained. In mucosal lesions, include some normal tissue as well as the lesion (biopsies of ulcers alone are inadequate) (Fig. 3.4). When a vesiculobullous disorder is suspected, include perilesional tissue and use a scalpel rather than a punch



Fig. 3.4 Punch biopsy

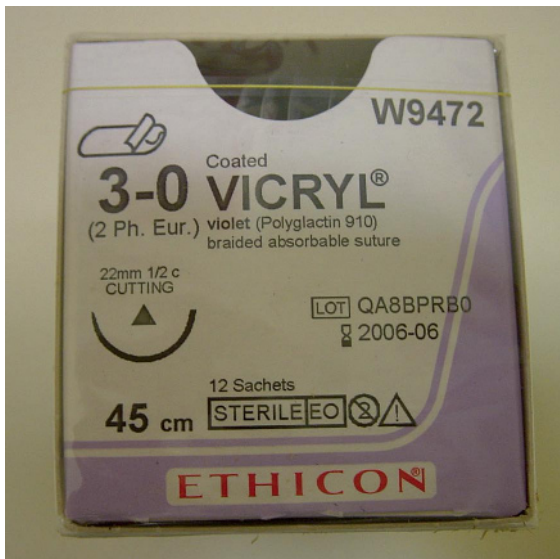


Fig. 3.5 Absorbable suture for biopsy closure

- do not squeeze with forceps as this can cause crush artefacts. Sutures may be used to hold the tissue and also to mark specific areas of biopsy
- place the biopsy specimen onto a small piece of paper before immersing in fixative, as this prevents curling. Put small specimens for histological examination immediately into buffered formalin or other fixative in at least its own volume of fixative, preferably 10-fold more, and leave at room temperature (20°C). A further biopsy specimen (or half of a larger biopsy) should also be immediately snap-frozen (-70°C) if immunostaining or a frozen section is required. If bacteriological examination is required, for example in suspected tuberculosis, send a separate specimen without fixative

- suture if necessary, preferably using a fine needle and resorbable suture such as Vicryl 3/0 or Vicryl Rapide 4/0, which will not require the patient to re-attend for removal (Fig. 3.5). Non-resorbable sutures, such as silk, are also available
- Use of an inverted suture technique means that there is no knot left in the mouth to irritate the patient.

Immunostaining and immunofluorescence

Specimens for immunostaining should not be fixed in formalin, but must be handed immediately to laboratory staff for freezing, or immediately snap-frozen (on solid carbon dioxide or liquid nitrogen) and taken within an hour or so to the laboratory, or, occasionally put into Michel's solution if the specimen cannot be frozen:

- Direct immunofluorescence is a qualitative technique used to detect immune deposits (antibodies and/or complement) in the tissues. It is a one-stage technique, requiring patient lesional or perilesional tissue (Fig. 3.6). Immunostaining usually uses a fluorescein stain, which fluoresces apple green under ultraviolet light, and is termed 'immunofluorescence'. It is useful in the diagnosis particularly of vesiculobullous disorders, such as pemphigoid and pemphigus.
- Indirect immunofluorescence is a qualitative and quantitative technique used to detect immune deposits (circulating antibodies and/or complement) in the serum. It is a two or more stage technique requiring patient serum and animal tissue.

Oral smears for cytology

Prepared in this way, smears will keep for up to 3 weeks:

- Take smears with a wooden or metal spatula, or dental plastic instrument.
- Spread smears evenly on the centres of two previously labelled glass slides.
- Fix smears immediately in industrial methylated spirit. Do not allow to dry in air, as cellular detail is rapidly lost and artefacts develop.
- After 20 minutes of fixation the smears can be left to dry in the air or left in fixative.

Oral brush biopsy

The brush biopsy is performed without anaesthetic and using a brush designed to obtain a transepithelial specimen containing cells from all three layers of the epithelium: the basal, intermediate, and superficial layers. This feature distinguishes it from cytology, which samples cells only from the surface of a lesion. It is important to ensure that the brush penetrates to the basement membrane since the basal cell layer may be the only layer of the epithelium that contains abnormal cells within a potentially malignant or

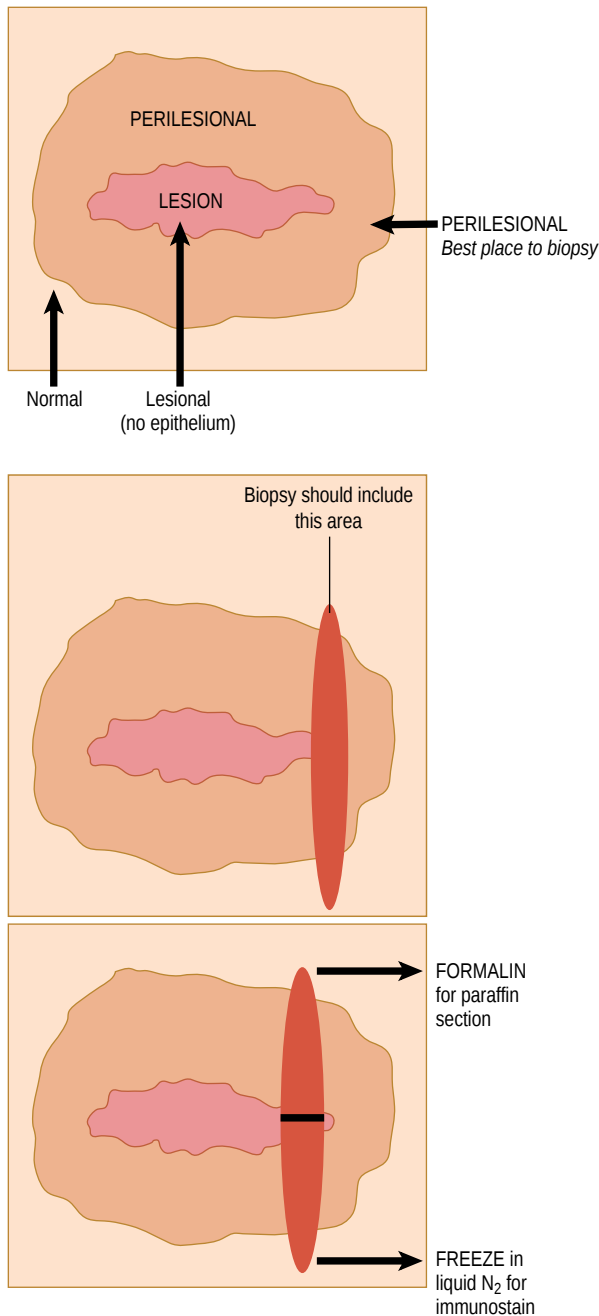


Fig. 3.6 Biopsy location

malignant lesion. This objective can be achieved by applying firm pressure when performing the brush biopsy procedure and rotating the brush on the lesion approximately 5–10 times, visualizing pinpoint bleeding or a pinkish-red mucosa at the site of the brush biopsy. The laboratory evaluates the specimen for adequacy by verifying by computer scan cellular representation from each layer of the epithelium. The computer does not give a final diagnosis, but assists in the identification and display of potentially abnormal cells, which are reviewed by pathologists.

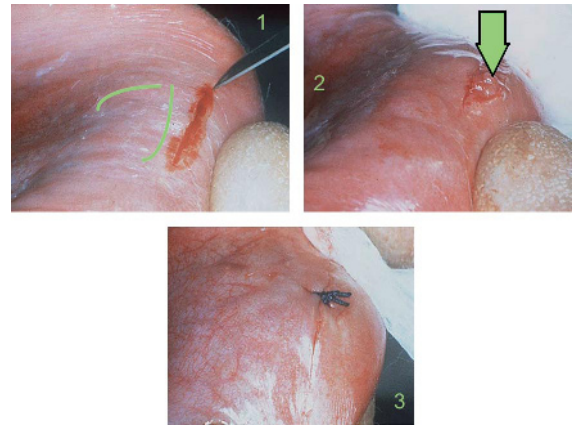


Fig. 3.7 Labial salivary gland biopsy

Lymph node biopsy

Lymph nodes should not be subjected to open biopsy if malignant disease is suspected: FNAB or FNAC are better, or the biopsy deferred until the time of operation.

Labial salivary gland biopsy

- Warn the patient of possible postoperative mild hypoesthesia.
- Give the patient local analgesia.
- Make a linear mucosal incision about 5–8mm long (to one side of the midline in the lower labial mucosa) or an x-shaped incision over the swelling, which overlies the salivary gland (Fig. 3.7).
- Excise at least four lobules of salivary gland.
- Suture the wound if necessary.

Frozen sections for rapid diagnosis

This procedure, in which the section is examined whilst the patient is still under anaesthesia, is useful in cases where malignancy is suspect and in resections, to check the resection margin for tumour infiltration and to assess whether the margins are tumour-free.

Communicate with the pathologist at the latest by the day before the operation. Specimens should be immediately snap-frozen (on solid carbon dioxide or liquid nitrogen) and taken immediately to the laboratory, or collected by the pathology team. Telephone the laboratory when the specimen is on its way. Warn the pathologist about any tissue containing calcified material that could break the microtome. The results should be transmitted by the pathologist to the clinician direct.

Radiography

Because of the adverse effects of ionizing radiation and the cumulative effect of radiation hazard, all investigations using X-rays must be justified by benefiting

Table 3.3
Investigative procedures in diseases of the jaws and sinuses

Procedure	Advantages	Disadvantages	Remarks
Transillumination	Simple	—	Helpful to show a fluid level
Fibre-optic endoscopy	Simple; good visualization	Skill needed	Useful to examine nasal passages, pharynx and larynx
Radiography	Reveals much data not obvious on clinical examination	Specialized techniques may be difficult	Upper occlusal radiography is useful for detecting cysts. Other radiographic views may fail to show cysts and diagnosis of a cyst can be very difficult if the antrum is large with outpouchings into the alveolar process and zygomatic bone, since these antral extensions may resemble cysts. Occipitomental radiography (Waters) views of the skull are the best radiographs for viewing the antra. These views can be taken at 15° and 30°, and can show an opaque antrum, a fluid level or fractures
Computerized axial tomography (CAT scan) and magnetic resonance imaging (MRI)	Reveal data often not seen on clinical or conventional radiographic examination	Expensive and not universally available. Interpretation requires additional training	Demonstrate both hard and soft tissues and give spatial relationships. Coronal CAT of the antrum can be useful for showing the extent of a neoplasm, particularly in the posterior and superior maxilla. CAT and MRI are useful particularly in detecting the extent of spread of a malignant neoplasm and have the great advantage of demonstrating the posterior maxilla, the intratemporal fossa, the floor of the orbit and the nasosphenoidal sinuses – sites not readily seen by other imaging
Aspiration	Simple	May introduce infection	May show the presence of haemangioma. The protein content of cyst fluid may be of diagnostic value (protein levels below 4g% in keratocysts)
Bone biopsy	Definitive	Invasive	
Bone scan	Surveys all skeleton	Those of any radionuclide procedure	May reveal pathology (e.g. metastases or osteomyelitis)

the patient. The clinician requesting the examination or investigation must satisfy himself that each investigation is necessary and that the benefit outweighs the risk.

Ionising Radiation Regulations (1988) required exposure of patients to be 'As Low As Reasonably Achievable' (ALARA) and have been superseded by the Ionising Radiation Regulations (1999) (IRR99) and Ionising Radiation (Medical Exposure) Regulations (2000) (IR(ME)R2000).

Radiography

The request form for radiography should be completed and signed by the clinician and should include the following:

- Vital patient data: full name, address, date of birth, unit number, ward, clinic or outpatient department and specialist in charge.
- Details that facilitate correct investigations and accurate opinion:
 - investigations required (region to be examined and, where relevant, special investigation needed)
 - diagnostic problem
 - relevant clinical features
 - known diagnoses
 - previous relevant operations.
- Other information, for example, whether the patient is a walking or trolley case, whether an urgent or routine report is required, the date, place and type of previous radiographs.

Table 3.4
Investigative procedures in temporomandibular joint disease

Procedure	Advantages	Disadvantages
Radiography	Simple Can reveal much pathology	Persistent lesions of uncertain aetiology
CAT scan	Can provide excellent information	Expensive
Arthrography (double contrast)	Provides excellent information	Danger of introducing infection Painful
Magnetic resonance imaging (MRI)	Provides excellent information without exposure to ionizing radiation	Non-invasive Expensive and not universally available
Arthroscopy	Minimally invasive Good visualization	Requires anaesthesia Technically demanding

A protective lead apron having a lead equivalence of no less than 0.25mm is worn by the patient only where the primary X-ray beam can strike the pelvis, such as in vertex-occlusal radiography, and a neck shield is indicated if the thyroid is to be exposed.

A particular problem arises during pregnancy, because of the hazard to the fetus. Enquiry as to pregnancy must always be made (risk of fetal irradiation) before performing radiography or other imaging procedures that involve radiation exposure by the primary beam to the abdomen and pelvis. Although most dental radiography does not constitute a risk, the clinician should always ascertain whether a woman is pregnant before requesting a radiograph and the investigation required should be discussed with the patient, who may wish to defer it until after pregnancy.

Note whether the patient:

- is of child-bearing potential
- is taking the contraceptive pill
- has had a hysterectomy
- has been sterilized.

Restricting X-ray investigations on women of child-bearing age to the 10 days following the start of a menstrual period (the 10-day rule) should be considered only for examinations with a relatively high gonad radiation risk, and has now fallen somewhat into disfavour.

Portable X-rays

- The quality of portable films is rarely as good as that of corresponding films taken using non-portable equipment.
- Examination should take place in the ward only if there is an absolute contraindication to the patient being brought to the radiography department. If there is any doubt about the advisability of bringing the patient to the department, consult a radiologist.
- Theatre radiography is done only when its results are needed during the operation.

Plain radiography

This is useful in the diagnosis of fractures, dislocations, bone and tooth disorders, joint disease and foreign bodies.

Chest radiography

The chest radiograph is valuable in investigating chest disease, heart disease (e.g. heart failure) and general medical problems, such as malaise, fever or weight loss (e.g. bronchial carcinoma, tuberculosis and other chest infections). Spinal computed tomography is a major advance.

Abdominal radiography

Abdominal radiographs are valuable in the diagnosis of gastrointestinal obstruction or perforation, renal stones or gallstones.

Intra-oral radiography

- Periapical radiographs are useful for demonstrating pathology in the periapical region (abscess, granuloma, cyst, etc.) and in tooth root, periodontium and adjacent bone.
- Bitewing radiographs show both upper and lower premolar and molar teeth on one film, but do not show the tooth apex. They are useful for revealing approximal caries and demonstrating the alveolar crest.
- Occlusal films may be useful in assessing the facial and lingual cortices and adjacent areas.

Dental panoramic tomography (DPT) [or orthopantomography (OPTG)]

This is valuable as a general survey and typically shows the antra and temporomandibular joints well. The radiation dose is considerably lower than a full mouth survey using periapical films, but it:

- lacks the detail obtained by other films, such as periapical radiography

Table 3.5
Investigative procedures in salivary gland disease

Procedure	Advantages	Disadvantages
Sialometry* (salivary flow rates)	Simple rapid clinical procedure which may confirm or refute xerostomia	Somewhat imprecise Wide range of normal values
Sialochemistry	Laboratory investigation; useful mainly in Sjögren syndrome	Salivary composition varies with many factors Far less useful than blood and other tests
Blood tests	Simple and can reveal systemic disease (e.g. rheumatoid arthritis)	Will not usually reflect local disease of salivary glands
Plain radiography	Lower occlusal and oblique lateral or OPT may show submandibular calculi Soft PA film may show parotid calculi	Calculi may not be radio-opaque Sialography may be needed
Sialography	Useful to eliminate gross structural damage, calculi or stenoses	Time consuming and somewhat crude and insensitive May cause pain or, occasionally, sialadenitis† Uses X-rays
Salivary gland biopsy	Labial gland biopsy is simple and may reflect changes in other salivary (and exocrine) glands Major gland biopsy and needle biopsy may be useful	Invasive Major gland biopsy may result in facial palsy or salivary fistula
Scintigraphy and radiosialometry	Measures uptake of radionuclide‡ (radiosialometry more quantitative) High uptake (hotspots) may reveal tumours	Expensive and with hazards associated with use of radionuclides Taken up by thyroid gland; rare instances of thyroid damage
Magnetic resonance, CAT scanning, ultrasound	Useful for investigating space-occupying lesions	Expensive, and not universally available

*Unstimulated whole salivary flow rates are usually used; flow rates of less than 1.5ml/15 min are low. Alternatively, stimulate parotid salivary flow with 1ml 10% citric acid on to tongue; flow rates of less than 1ml/min may signify reduced salivary function. Alternatively, pilocarpine 2.5mg i.v. may be used, but is contraindicated in cardiac patients or those with hypertension.

†Combined sialography with CAT scanning may be useful in the diagnosis and localization of salivary gland lesions, particularly parotid neoplasms.

‡Usually technetium pertechnetate.

- does not show detail in the anterior jaws
- does not show caries until this is advanced
- can result in ghost shadows and blurring
- examines only a slice of tissue.

Radiovisigraphy

Radiovisigraphy (RVG) is digital imaging, and is useful in reducing the radiation exposure, particularly where there is a need for repeated films, such as in endodontics.

Sialography

Sialography involves instillation of radio-opaque contrast media into the salivary duct followed by oblique lateral and postero-anterior (PA) or rotated PA

radiographs. Use of a sialogogue, such as lemon juice, to empty the gland gives an 'emptying film'. Sialography can sometimes help to:

- assess patients with xerostomia
- assess patients with salivary swelling
- detect ductal obstruction
- detect the rare cases of salivary aplasia.

Arthrography

Arthrography involves injection of radio-opaque contrast media (usually iohexol or iopamidol) into the lower space of the temporomandibular joint. The main indication is in suspected internal joint derangements.

Table 3.6
Investigative procedures in oral mucosal disease

Procedure	Advantages	Disadvantages	Remarks
Biopsy	Gives definitive diagnosis in many instances	Invasive	Mucosal biopsies should be submitted for histopathological and often direct immunofluorescence examinations if a vesiculobullous disorder is suspected
Brush biopsy	Simple, non-invasive procedure	Possible false-negative results	Helpful in review of widespread potentially malignant lesions
Bacteriological smear and culture	Simple clinical procedure	Isolation of organisms does not necessarily imply causal relation with disease under investigation. Some organisms are non-cultivable.	Anaerobic techniques may be indicated especially in oral lesions in the immunocompromised host
Fungal smear	Simple clinical procedure	As above	Candida hyphae suggest Candida species are pathogenic
Viral culture	Simple sensitive clinical procedure Often gives diagnosis more rapidly than does serology	May require special facilities and may only give retrospective diagnosis	False-negative results possible Indicated in some acute ulcerative or bullous lesions Serology should also be undertaken
DNA studies	Polymerase chain reaction often used	May require special facilities	Rapid and specific results
Haematological screen, haemoglobin red cell and white cell indices	Simple clinical procedure	Detection rate may not be high	Essential to exclude systemic causes of oral disease, especially ulcers, glossitis or angular stomatitis
Serology	Demonstration of a rise in titre-specific antibodies between acute and convalescent serum may be diagnostically useful Specific tests available, e.g. HIV antibodies	Serum autoantibodies may not mean disease Serum autoantibodies may be undetected in pemphigoid Diagnosis of viral infections is retrospective	Essential in suspected HIV, connective tissue disease, autoimmune or other immunological disorders

Angiography

Angiography involves injection of radio-opaque contrast media into arteries (arteriography) or veins (venography). The main indications include:

- diagnosis or delineation of vascular anomalies or tumours
- assessment of tumours in the deep lobe of the parotid gland
- assisting surgical procedures (e.g. microvascular surgery or embolization).
- has considerable advantages for visualizing complex anatomical areas inaccessible to conventional radiographs
- is particularly useful for assessing pathology in the head and neck, especially for determining tumour spread, to exclude cranial base or intracranial pathology and planning surgery and implant placement
- is good for visualizing hard tissue lesions mainly
- gives a fairly high radiation exposure (CT of the head can give the equivalent exposure to about 100 chest radiographs)
- is expensive.

Computed axial tomography

Computed axial tomography (CAT or CT) integrates information from multiple radiographic 'slices' into images of internal tissues (e.g. brain, orbit, sinuses, neck). It:

Scintiscanning (radionuclide scanning)

Radioactive pharmaceuticals with affinity for specific organs or tissues can be detected and measured by a gamma camera.

Table 3.7
Imaging available for lesions in different locations

Location of lesions	Plain radiography	Other imaging
Mandible	Rotational tomography Oblique lateral Computed tomography (CT)	Magnetic resonance imaging (MRI) Bone scan
Mandibular condyle	Reverse Towne's Submentovertex CT	MRI Bone scan
Temporomandibular joint	Rotational tomography Transcranial CT Transpharyngeal CT	MRI Arthrography Bone scan
Maxilla	30 occipitomeatal CT	MRI Bone scan
Paranasal sinuses	OM rotational tomography for maxillary antra Upper occlusal or lateral Submentovertex CT	MRI Bone scan
Skull	PA skull rotational tomography 10 occipitomeatal Lateral skull CT	MRI Bone scan
Salivary glands	Oblique lateral Rotated PA CT	Sialography Scintigraphy Ultrasound MRI
Intra-oral	Rotational tomography CT	Ultrasound MRI

Salivary scintigraphy

Intravenous sodium pertechnetate is taken up by salivary glands and secreted in saliva. Scintiscanning can be useful in the diagnosis of:

- Sjögren syndrome
- ductal obstruction
- salivary neoplasms
- salivary aplasia.

It may also help locate a lingual thyroid.

Bone scans

Intravenous technetium methylene diphosphonate is taken up by osteoblasts, and bone scans can be useful in:

- assessing condylar or coronoid hyperplasia
- detecting metastases
- detecting bone invasion
- determining activity of fibro-osseous or other bone disease.

Positron emission tomography

Positron emission tomography (PET) produces maps of brain metabolic activity based either on blood flow or glucose utilization.

Non-radiation imaging

Magnetic resonance imaging

Magnetic resonance imaging (MRI) does not involve ionizing radiation. MRI depends on the distribution of protons (hydrogen nuclei) in tissues and their effect on a magnetic field. The MRI signal has two components:

- T1, in which the proton is spinning under magnetic influence and radiofrequency to return to the original value (spin lattice or longitudinal relaxation time)
- T2, which depends on the gradual dephasing of the protons in the transverse or transaxial plane (spin-spin, or transverse relaxation times).

The advantages of MRI are that it is:

- especially good for visualizing soft tissues and lesions
- useful for imaging the temporomandibular joint
- good for revealing bone invasion.

The disadvantages of MRI are that it is:

- not good for imaging bone

Table 3.8
Significance of the more common autoantibodies

Autoantibody	Main significance*
DNA antibodies [ds-DNA (<i>Crithidia luciliae</i>)]	Systemic lupus erythematosus
Nucleolus-specific RNA	Scleroderma
Sc1-70 (anti-topoisomerase)	Scleroderma
Rheumatoid factor	Rheumatoid arthritis (RA) (sometimes systemic lupus erythematosus)
Robert (Ro), also known as soluble substance A antigen (SS-A)	Sjögren syndrome
Lane (La), also known as soluble substance B antigen (SS-B)	Sjögren syndrome
Epithelial intercellular cement (desmoglein)	Pemphigus
Epithelial basement membrane zone (e.g. integrin)	Pemphigoid**
Parietal cell antibody; intrinsic factor antibodies	Pernicious anaemia

*The presence of autoantibodies does not always indicate disease

**or other immune-mediated subepithelial blistering diseases

- fraught with producing image artefacts where metal objects are present (dental restorations, implants, orthodontic appliances, metallic foreign bodies, joint prostheses, etc.)
- expensive.

Contraindications to the use of MRI include:

- implanted electric devices, such as pacemakers, nerve stimulators, cochlear implants
- intracranial vascular clips, if these are ferromagnetic
- prosthetic cardiac valves containing metal.

Thus, MRI gives sensitive images of the internal organs and tissues (e.g. brain or spine), but it cannot be used in the presence of metal (e.g. orthodontic fixed or removable appliances, dental endosseous implants or metal-containing prostheses).

Ultrasound (US) scanning

- Ultrasonography involves high frequency sound waves (2–15MHz) with wavelengths of 0.6–0.01 mm, and does not involve ionizing radiation exposure.
- When the sound strikes the interface between media, the energy reflects as an echo, which may be displayed as a unidimensional wave image (an A scan) or, when a sweeping beam is used, as a two-dimensional monochrome image (a B scan). Colour Doppler ultrasound (CDUS) may be useful.
- Abrupt impedance occurs with calcified lesions, or foreign bodies, such as glass or metal.
- Ultrasound, therefore, gives useful imaging of soft tissues and internal organs (e.g. lymph nodes or salivary glands) and foreign bodies.

- Doppler ultrasound is also useful for investigating vascular disease.

Thermography

An infrared camera detects areas of changed vascularity, but has the disadvantage of needing the patient to be 'precooled'.

Photography

This is exceedingly useful to record lesions, and the advent of digital photography has considerably improved the quality.

Investigations of specific medical problems

Anaemia

Anaemia is caused mainly by:

- reduced erythropoiesis
- haemolysis or
- haemorrhage.

The most usual cause of anaemia in the developed world is iron deficiency caused by chronic haemorrhage (commonly menorrhagia). After a thorough history and examination, the following are required for diagnosis of the extent and type of anaemia:

- haemoglobin concentration
- a full blood film
- red cell indices
- white cell count and differential.

The cause must then be established.

Deficiency anaemias

Once the type of anaemia has been established, the cause must be found and treated. In iron deficiency, unless it is clear that menorrhagia is the cause, the site of blood loss should be sought, usually in the gastrointestinal tract:

- Iron deficiency anaemia is usually microcytic [mean corpuscular volume (MCV) reduced] and managed by treatment of the cause, and iron supplements. Only rarely is transfusion necessary, usually when the haemoglobin is less than 9g/dl and surgery is required urgently. Packed red cells should be used in preference to blood.
- Folate deficiency is commonly dietary in origin. Folate or vitamin B₁₂ deficiencies may result in a macrocytic (megaloblastic) anaemia (MCV raised). Treatment of folate deficiency is with folic acid.
- Vitamin B₁₂ deficiency is rarely dietary in origin; more commonly, it is caused by a gastrointestinal lesion or pernicious anaemia. Treatment is with vitamin B₁₂, usually by injection for life.
- Deficiencies of multiple haematinic factors, e.g. iron, folate and vitamin B₁₂, may well be caused by disease of the small intestine, such as coeliac disease (gluten-sensitive enteropathy).

Sickle cell anaemia

Sickle cell anaemia is:

- a hereditary condition affecting haemoglobin [sickle haemoglobin (HbS)]
- characterized by the fact that the red blood cells may adopt a sickle shape, especially in hypoxia
- found mainly in patients of African heritage and some originating from the Mediterranean countries and Asia
- a risk for general anaesthesia.

Rule out sickle cell anaemia in all black patients and record results to prevent unnecessary re-testing:

- Check the medical history.
- Do a full blood picture.
- Do a screening test, such as a simple solubility test (e.g. the SickDex test). This will detect the presence of any HbS in the blood and is, therefore, positive both in patients with sickle cell anaemia and the trait (see below).
- Further haematological examination, including haemoglobin electrophoresis, is theoretically

required for confirmation. In practice, however, a positive solubility test with a low haemoglobin level can be taken as being diagnostic of sickle cell anaemia. A positive solubility test with a normal haemoglobin level may indicate the sickle cell trait (see below).

Homozygous form: sickle cell anaemia

In the homozygous form, at low oxygen tensions (about 45mmHg), the red cells become inelastic and sickle shaped. The erythrocytes then either 'sludge', blocking capillaries and causing infarcts (e.g. in bone and brain), or rupture, causing haemolytic anaemia.

Heterozygous form: sickle cell trait

In patients with the sickle trait, sickling occurs only at much lower oxygen tensions (below 20mmHg), which are unlikely to occur in normal clinical practice.

Bleeding tendency

Screening tests typically include:

- platelet count
- function tests
- APTT (activated partial thromboplastin time)
- PT (prothrombin time) and international normalized ratio (INR) – the ratio of the patient's PT to a control
- clotting factor assays.

Screening tests will eliminate two-thirds of suspected cases, and the remaining third will require more detailed tests to accurately define a diagnosis. Consult the haematologist immediately before undertaking other investigations; bleeding and clotting times are quite unsatisfactory, and special investigations may well be required, such as factor VIII clotting activity or related antigen assay.

Endocrine disorders

Adrenocortical function testing

- Blood pressure: is low in hypoadrenocorticism, high in hyperadrenocorticism.
- Plasma cortisol levels: the diurnal rhythm of plasma cortisol is a sensitive index of adrenal function; plasma cortisol values are normally highest between 6.00 and 10.00 a.m. and lowest between midnight and 4.00 a.m. Samples taken at 8.00 a.m. and 4.00 p.m. should differ by at least 5mg/100ml. The sample taken at 8.0 a.m. should be 5–25mg/100ml. Plasma cortisol at 8.00 to 9.00 a.m. is often below 6mg/100ml in hypoadrenocorticism. Diurnal variation in cortisol is lost in hyperadrenocorticism.

Table 3.9
Glandular fever syndromes

Syndrome	Causal agents	Investigations
Infectious mononucleosis (classic glandular fever)	Epstein-Barr virus (EBV)	Paul-Bunnell test (heterophile antibodies) EBV antibodies
EBV-negative glandular fever	Cytomegalovirus (CMV)	CMV antibodies
Acute HIV seroconversion	Human immune deficiency viruses (HIV)	HIV antibodies Lymphopenia T4 (CD4) cell depletion
Erythema subitum	Human herpes 6	HHV-6 antibodies
Toxoplasmosis	<i>Toxoplasma gondii</i>	Sabin-Feldman dye test – specific IgM antibodies

- Synacthen test (ACTH stimulation test): this is performed in the following way. Take blood at 8.00 to 9.00 a.m. for the plasma cortisol level; give 0.25mg Synacthen subcutaneously or intramuscularly; after 30 minutes, take a further blood sample for the plasma cortisol level. Normally, Synacthen results in a rise in cortisol levels to over 18mg/100ml. This rise is lost in hypoadrenocorticism (at an earlier stage in disease than the low cortisol level is found).
- Abdominal radiography: this may show calcified adrenals if tuberculosis is the cause of hypoadrenocorticism.
- Serum autoantibodies: patients with Addison's disease may have various circulating autoantibodies.
- Electrolytes: plasma potassium is raised and sodium reduced in Addison's disease.

Diabetes

Diabetes is often detected at routine urinalysis by detecting glycosuria (and ketonuria), but there are other causes of glycosuria and of ketonuria, and diabetics do not always have glycosuria.

Diabetes is best diagnosed by testing for raised blood glucose either in the laboratory, or at home with a glucometer. Blood is collected for laboratory, testing in a special fluoride-containing bottle. A random whole blood glucose above 11mmol/l or fasting level over about 7mmol/l usually establishes the diagnosis (plasma glucose levels are about 1mmol/l higher). Glucose tolerance testing is indicated only if blood sugar values are borderline. A widely accepted simplified glucose tolerance test (GTT) is as follows: give the patient 75g glucose orally; assay blood glucose levels 2 hours later; a level greater than 11.1mmol/l is diagnostic of diabetes; a level less than 11.1mmol/l excludes diabetes.

Diabetic control is best by serial measurements of blood glucose levels throughout the day with a glucometer. Glycosylated haemoglobin or fructosamine are usually monitored regularly to assess longer term control. Non-diabetics have up to 7% glycosylated haemoglobin:

7–9% represents good control, over 13% shows poor control in diabetes.

Previously patients controlled their diabetes by testing their urine at home and recording the degree of glycosuria with Clinitest tablets, Diastix or Diabus strips. However, glycosuria tested in this relatively crude way does not usually become detectable until the blood sugar level is about 10mmol/l (which already represents a considerable degree of hyperglycaemia), and it is, therefore, important to assess the renal glucose threshold to ensure that the measurement of glycosuria is not misleading as to blood glucose levels. This can be roughly estimated by comparing simultaneous urine and blood sugar concentrations.

The degree of ketosis can be rapidly assessed in the urine with Acetest tablets. A small amount of ketonuria, as shown by this test, is usually of no importance, but a strongly positive test, especially if confirmed by a positive ferric chloride reaction (Gerhardt's test), indicates a serious degree of ketosis. Confirmation is obtained by finding a low serum bicarbonate concentration.

Hyperparathyroidism

Blood for calcium levels should be collected early in the morning from a fasting patient. A tourniquet should not be used (venous stasis and a fall in pH alter calcium levels). The blood collection should be done along with serum for albumin assay (albumin levels influence calcium levels). This assay may need repeating several times to exclude hyperparathyroidism.

Sexually transmitted infections

HIV

Diagnosis of HIV disease is from other causes of glandular fever syndromes (Table 3.9) and includes:

- clinical features

- lymphopenia
- a severe T-helper lymphocyte defect (reduced CD4⁺ cells)
- HIV antibodies (serotesting after counselling)
- excluding other sexually transmitted infections.

Syphilis

Dark field microscopy of a lesion may demonstrate *Treponema pallidum*. Oral lesions should be washed first with saline to remove oral commensal treponemes. Also:

- serology is indicated
- the venereal disease research laboratory (VDRL) test is the screening test used
- since the VDRL test is not specific and may lead to false-positive results, a more specific test, such as the fluorescent treponemal antibody (FTA)-Abs or IgM-FTA-Abs, must be used where the VDRL test proves positive
- always exclude other sexually transmitted infections.

Gonorrhoea

Gonococcal pharyngitis may be seen, particularly in men who have sex with men. Take a direct smear for Gram-staining (Gram-negative diplococci) and also take a bacteriological swab from the area, for culture and sensitivities. Always exclude other sexually transmitted infections.

Hepatitis viruses B and C

Hepatitis B virus (HBV) and hepatitis C virus (HCV) tests include tests for antigens, antibodies and sometimes DNA. Patients positive for hepatitis B surface antigen (HB_sAg) should be screened for HB_eAg (e antigen).

About one in five are HB_eAg positive and at high risk of infectivity. Those who have HB_sAg should later be screened again at 3 months, and again if still positive. Those positive at 9 months are 'chronic carriers'.

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4

Treatment

Our universal aim should be to treat every patient as we would wish our families, or indeed ourselves, to be treated.

C Noyek

Introduction

Many of the conditions seen in oral and maxillofacial medicine practice have systemic manifestations, or they may be seen in patients with medical problems. It is crucial, therefore, always to collaborate closely with the medical and any other attendants in the care of the patient.

A specialist opinion may also be called for.

Referral to a specialist

Referral may be indicated when the practitioner is faced with:

- a complicated or serious diagnosis (especially cancer, HIV infection, pemphigus, Behçet disease)
- a doubtful diagnosis
- a patient who has extraoral lesions or other indications of possible systemic disease
- a situation where investigations are required, but not possible or appropriate to carry out in general practice
- a situation where therapy may not be straightforward and may require potent agents
- a situation where drug use needs to be monitored with laboratory or other testing (e.g. for liver functional disturbances)
- a patient who needs access to an informed opinion or care outside normal working hours.

Should referral be required, it should always be in writing, giving a concise background to the referral, including:

- referring clinician's name, address, telephone, facsimile and e-mail
- patient's surname
- patient's first name(s)
- patient's date of birth
- patient's full address and telephone, mobile phone, facsimile and e-mail where possible
- patient's medical practitioner's name, address and telephone, facsimile and e-mail
- urgency of referral (real or perceived)

- reason for referral
- relevant history
- relevant findings
- provisional diagnosis
- relevant medical history
- relevant social history
- treatment already offered
- any special needs.

Psychological and sociological aspects of treatment

Treatment is much more than the simple use of a drug or the performance of a procedure; the whole psychology of the patient is important. Remember always that patients know whether the clinician cares, well before they care whether the clinician knows all the answers.

Many orofacial conditions are chronic and have no cure, and for a few disorders the prognosis is poor or, fortunately rarely, the condition may even be lethal. Therefore, compassion and patient education and participation are important. Empowering patients allows them to take control of their lives and decisions affecting their wellbeing. Such education and reassurance is always helpful; a supportive and understanding clinician is invariably welcomed by the patient, their partner and their family.

It is important to:

- do no harm
- manage the patient as a whole, in the context of their individual perceptions, aspirations, general health and social setting
- offer hope. Not all conditions can be cured, but most can be controlled or at least ameliorated. General improvements in oral health also help control symptoms in several other orofacial disorders
- work with the patient and family, and involve the patient in all decisions. Discuss the condition, diagnosis and possible therapies with the patient (and possibly partner and family, provided the patient consents)
- warn of possible consequences (good and bad) of treatment or of no treatment
- obtain express informed consent before any invasive procedure
- offer advice on what patients themselves can do for their problems, including support from family, partners, friends and other bodies (e.g. alcohol, smoking)

or other drug support groups), disease support groups (e.g. cancer help groups or the Pemphigus support groups, or Sjögren Syndrome Society) or other information sources (e.g. patient information sheets, the internet).

Lifestyle changes

There is no doubt that certain lifestyle habits, such as the use of tobacco products, areca nut products and alcoholic beverages, should be discouraged, especially in patients with oral mucosal diseases. Indeed, sometimes, the cessation of these habits may lead to resolution of the condition. Diet and/or oral hygiene may also need changing.

Preventive care

Oral hygiene

Dental staff should ensure the patient has appropriate oral health education, and maintains particularly good oral hygiene, since the limited evidence available

suggests that good oral hygiene helps the resolution of some lesions as well as gingivitis.

The most important devices in oral hygiene are floss and a toothbrush; many are effective:

- soft toothbrushes and silica-based toothpastes are least abrasive
- electric toothbrushes may assist oral hygiene especially in those with impaired manual dexterity
- interspace and other toothbrushes can access areas difficult to clean.

Toothpastes are available that offer tooth whitening, plaque control (Fig. 4.1), desensitization, calculus (tartar) control, tooth remineralization and malodour control (Table 4.1).

Antiplaque agents are commonly used to reduce infection and malodours, particularly if the patient is immunocompromised. Many mouthwashes have only a transient antiseptic activity (Table 4.2), but:

- chlorhexidine digluconate is the most widely used antiplaque agent (Fig. 4.2) and is active, especially against Gram-negative rods, it helps control plaque and periodontal disease and has some anticaries and antifungal activity. It has good substantivity (ability to bind to hard and soft tissues and be released over a long period), but binds tannins and thus can cause dental staining if the patient drinks coffee, tea or red wine. Rarely, it causes other adverse effects, including:
 - overgrowth of enterobacteria (e.g. in leukaemic patients)
 - mucosal desquamation
 - hypersensitivity
 - salivary gland pain or swelling.
- triclosan is a chlorinated bisphenol with some substantivity and a broad spectrum of antibacterial



Fig. 4.1 A triclosan-containing dentifrice

Table 4.1
Various toothpastes (dentifrices)

Characteristic	Main UK trade name
Normal fluoride	Macleans Freshmint/Coolmint*
High fluoride	Colgate Triple Cool Stripe* Colgate Ultra Cavity Protection* Crest Complete*
Low fluoride	Macleans Milk teeth* Macleans Milk teeth gel*
Against sensitivity	Macleans Sensitive*
Against gingival disease/caries/tartar	Colgate Total* Crest Complete*
Whitening	Macleans Whitening Toothpaste*
No additives	Kingfisher

*Toothpastes accredited by the British Dental Association.

Table 4.2
Some mouthwashes with significant antimicrobial activity

Agent	Dose	Comments*
Chlorhexidine gluconate	0.12–0.2% aqueous mouthwash, rinse for 1 minute twice daily. Also 0.5–1.0% gel or spray	A cationic chlorinated bisbiguanide with significant antiplaque and antifungal activity and oral retention; traces can still be found in saliva after 24 hours. May stain teeth if patient drinks tea, coffee or red wine
Triclosan	0.03% mouthwash, rinse for 1 minute twice daily	A non-ionic chlorinated bisphenolic antiseptic with moderate antiplaque and antifungal activity, but less retention in mouth than chlorhexidine. More effective against plaque when with copolymer or zinc citrate
Cetylpyridinium chloride	0.05% mouthwash used twice daily	A quaternary ammonium compound with antiplaque activity, but less than chlorhexidine. May stain teeth and cause oral burning sensation or ulceration

*All occasionally may cause mucosal irritation.

activity, and a significant antiplaque effect, without staining the teeth.

- Phenolics, such as Listerine, have some antiplaque effect and do not stain teeth, but have low substantivity.
- Oxygenating mouthwashes may have a place in the control of anaerobic infections, such as necrotizing gingivitis.
- Sanguinarine is marketed for activity against bacterial plaque and malodour, but with low activity in these respects. A toxic alkaloid extracted from some plants, including Bloodroot (*Sanguinaria canadensis*), Mexican Prickly Poppy (*Argemone mexicana*), *Chelidonium majus*, and *Macleaya cordata*, it has, however, also been incriminated in some oral white lesions.

Caries prevention

A low cariogenicity diet is important (see below). Fluoride is also helpful for anticariogenic activity, especially useful for patients with dry mouth (Table 4.3, Figs 4.3–4.6). Chewing gum may stimulate salivation and help caries prevention and malodour (Fig. 4.7).

Diet

A healthy balanced diet is indicated to help resolution of oral conditions. In particular:

- many mucosal lesions are aggravated by irritants, such as tobacco and alcohol, and these also decrease salivary flow and should thus be avoided
- a softish diet, avoiding toast and potato crisps, spices and acids, such as in tomatoes and citrus fruits, may be indicated for a short period whilst a patient has a sore mouth and pureed non-irritant foods and cool moist fruits, such as melon, are helpful in persons with dry mouth or soreness.
- although vitamin and iron deficiencies are not common, supplements may be required if the diet is lacking



Fig. 4.2 A chlorhexidine-containing mouthwash

- dietary control and fluoride use is essential in xerostomia, to avoid caries. Fluorides may be usefully applied in the dental office, and daily at home (1% sodium fluoride gels or 0.4% stannous fluoride gels). Young children may need fluoride supplements if their water supply has a low fluoride content.

Symptomatic care

Specific therapies are not available for all conditions, and the best that can then be offered is the control of symptoms; this is called symptomatic treatment. Local antiseptics (e.g. chlorhexidine) may aid resolution of mucosal lesions. Attention should be directed to relieving the following (Table 4.4):

- Pain and discomfort: topical agents, such as 0.1% benzydamine mouth rinse or spray, may help symptomatically (Fig. 4.8). Antipyretics/analgesics,

Table 4.3
Regime for caries prevention

Eliminate active caries	Restorative dental care
Preventive measures	Patient education Dietary modification Fluorides; 1.23% acidulated fluoride or 2% neutral fluoride gels in 4-minute tray applications 4 times daily over 4 weeks; or home fluoride applications by gels or rinses Xylitol chewing gum; chew for 5 minutes 5 times daily Chlorhexidine mouthwashes; 0.2% used twice daily for 1 minute
Examine at 3 monthly recall appointments	Reinforce preventive message Monitor restorations Monitor cariogenic micro-organisms (<i>Streptococcus mutans</i> testing)



Fig. 4.3 A fluoride daily mouthwash



Fig. 4.4 A fluoride weekly mouthwash

such as paracetamol/acetaminophen, help relieve pain (Fig. 4.9) and a soft diet may help. Erosive or ulcerative lesions can be protected with Orabase or Zilactin.

- Fever: paracetamol/acetaminophen helps relieve fever and adequate fluid intake is important.
- Malodour (Ch. 9, page 87).
- Anxiety: patient information is an important aspect in management and goes a long way to relieve anxiety, but there may need to be recourse to mild anxiolytics, such as diazepam 2.5mg or temazepam 5mg.

Surgery

This can range from the simple excision of a lump such as a papilloma, to removal of a tooth, or to resection of a malignant neoplasm. Referral to a surgeon may be indicated:

- All surgery is invasive
- Scalpel, laser or electrosurgery are available

- Only an operator adequately skilled in a procedure should perform it.

Other less-invasive or non-invasive treatments

These include:

- cryotherapy
- soft laser therapy
- photodynamic therapy
- appliances (e.g. splints, tissue conditioning).

Follow-up of patients

Though it is desirable to offer treatment for oral lesions, this is not always possible or indicated, and sometimes watchful waiting is required, by following up



Fig. 4.5 A fluoride gel

the patient. Sometimes, for example in suspected traumatic ulceration, the diagnosis can only be decided by removing predisposing factors, and then checking progress in 2 weeks to see if the lesion is healing.

Drug treatment

Always remember the following:

- Use the safest drugs; virtually all drugs can have some adverse effects. Use only drugs with which you are totally familiar and use their generic (non-proprietary) drug names.
- Check that the prescription is legible and that there is no history of allergy or untoward effect. Always check drug doses, contraindications, interactions and adverse reactions.
- Warn the patient of, and discuss, possible adverse effects.



Fig. 4.6 A fluoride extra strength gel



Fig. 4.7 A chewing gum

- Reduce drug doses when prescribing for children, the elderly and patients suffering from liver disease and kidney disease.
- Consider the possibility of altered drug metabolism. The cytochrome P450 system of enzymes in the gastrointestinal mucosa and liver metabolizes many drugs, and various P450 isoenzymes (CYP isoenzymes) metabolize drugs by oxidation, typically reducing their effect. CYP isoenzymes may have different activities between individuals and ethnic groups; this increases, for example, the activity of some anxiolytics such as diazepam (up to 6% of whites, but up to 23% of Asians are sensitive to diazepam). Antidepressants and analgesics may also be affected:
 - Some drugs, for example erythromycin, inhibit CYP leading to the reduced ability to metabolize drugs, such as ciclosporin.
 - Grapefruit juice contains flavonoids that can inhibit CYP and thus increase the activity of, for example, ciclosporin and some protease inhibitors.
 - Some over-the-counter (OTC) herbal preparations, such as St John's Wort, can induce CYP; they can thus reduce the effect of protease inhibitors, antidepressants, warfarin, anticonvulsants and the contraceptive pill.
- Alcohol and smoking can affect CYP.
- Avoid drug use in pregnancy, where possible.
- Avoid giving aspirin to children under 16 years of age, because of the risk of Reye syndrome.
- Avoid aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) in patients with peptic ulcers, or bleeding tendencies such as haemophilia or thrombocytopenia and in those taking anticoagulant drugs, since they exacerbate bleeding.
- Avoid metronidazole, azoles and some other antimicrobials in patients on warfarin, since they displace it from plasma proteins and increase bleeding.

Table 4.4
Agents that may reduce pain from mucosal lesions

Agent	Use
Benzylamine hydrochloride	Rinse or spray every 1.5–3 hours
Lidocaine	Topical solution may ease pain
Carboxymethylcellulose	Paste or powder used after meals to protect area



Fig. 4.8 Oral rinse benzylamine.



Fig. 4.9 Acetoaminophen tablets.

- Avoid tetracyclines in pregnancy or breast-feeding, as they cause tooth discolouration.
- Avoid intramuscular injections in patients with bleeding tendencies, such as haemophilia or thrombocytopenia, and in those taking anticoagulant drugs, as haematomas can result, and take care with surgery.
- Take care if surgery will involve bone in patients who have been on bisphosphonates, as osteonecrosis can result, or in patients who have been irradiated in the head and necks (osteonecrosis can arise).

Table 4.5
Rough guide for prescribing for children

Age of child (years)	Percentage of adult drug dose
1	25
6	50
12	75

In the UK, the British National Formulary (BNF), published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain, which includes the Dental Practitioners' Formulary (DPF) is a valuable source of information and advice on therapy. The BNF is revised twice yearly, and only the current issue should be consulted; it is available on the internet. Hand-held devices, such as the Palm Pilot, have software such as Epocrates, which holds comprehensive drug data.

Prescribing for children

- Doses of all drugs are much lower for children than for adults; always check against the recommended dose per unit body weight (Table 4.5).
- Some drugs are contraindicated (e.g. tetracyclines are contraindicated under the age of 7–8 years; also, aspirin is contraindicated in all children under 16 years old).
- Some drugs (e.g. diazepam) are best avoided as they may have anomalous effects.
- Oral preparations are invariably preferable to injectable drugs.

Prescribing in pregnancy and during breast-feeding

Because of the danger of damage to the fetus, all drugs should be avoided in pregnancy, unless their use is essential. In particular avoid tetracyclines, which stain teeth, and retinoids and thalidomide, which are teratogenic.

Prescribing for the elderly

- Lower drug doses are almost invariably indicated.
- Compliance may be poor.

- Care should be taken when there is the possibility of renal or hepatic dysfunction; this will necessitate reduced doses.

Drugs and food absorption

Most oral drugs are best given with or after food. Oral drugs that should be given at least 30 minutes before food, since their absorption is otherwise delayed, include:

- aspirin
- erythromycin
- paracetamol/acetaminophen
- penicillins (including ampicillin and amoxicillin)
- rifampicin
- tetracyclines (except doxycycline).

Grapefruit juice disturbs the absorption and metabolism of some drugs and, therefore, should be avoided by persons taking:

- ciclosporin,
- calcium channel blockers (e.g. nifedipine)
- terfenadine.

Prescribing in different cultures

Some key concerns for different groups of patients are set out in [Table 4.6](#).

Gelatin is made of protein derived from animal bones, cartilage, tendons and other tissues, such as pig skin. The other most commonly used agents of animal derivation are insulin, heparin and haemostatic agents, such as blood coagulation factors and topical agents.

Most oral healthcare products are licensed only as 'cosmetics', which are less rigorously tested than pharmaceutical products, although they must still be labelled with all active and inactive ingredients. Toothpastes fall into this category. Some oral health care products are licensed as pharmacological products and because they must be labelled with all ingredients – active and inactive, and this readily affords the opportunity to avoid certain religious and ethnic group restrictions.

Some mouthwashes contain colourants or excipients that may be animal derivatives and many contain alcohol, which may raise objections on religious grounds, although the objections are not always well-founded, when the religious rules are consulted.

Some toothpastes may contain 'glycerin', manufactured synthetically or derived from animal fat, and this may not be included in the ingredients. Such toothpastes may be contraindicated for use on religious or cultural grounds.

Some artificial saliva preparations contain animal mucin, which may be unacceptable on religious grounds

to some Muslims, Hindus, Jews and Rastafarians. Products containing carboxymethylcellulose may then be preferred.

Oral healthcare products that might contain animal derivatives could include some:

- analgesics
- antimicrobials
- bone fillers
- colorants
- drug capsules
- emulsifiers
- haemostatic materials
- polishing (bristle) brushes
- prophylaxis pastes
- waxes.

Adverse reactions to drugs

Almost any drug may produce unwanted or unexpected adverse reactions and some produce oral adverse reactions. The true incidence of adverse drug reactions is often not known, and many adverse reactions are probably not, at present, recognized as drug-related. A full medical history should always be taken and questions should be asked specifically about drug use (including over-the-counter preparations) and adverse drug reactions, since the medical status may influence the choice of drugs used. Polypharmacy should be avoided and practitioners should use only drugs with which they are familiar.

Patients should be warned if serious adverse reactions are liable to occur (e.g. systemic corticosteroids), and provided with the appropriate warning card to carry.

No drug should be used unless there are good indications. After injections, there is a small chance that anaphylactic shock may occur.

Subcutaneous injection of drugs

This is used for injection of drugs such as:

- local anaesthesia
- epinephrine (adrenaline)
- insulin
- heparin
- opiate analgesics.

Subcutaneous injections can be given into a skin fold, pinched up over the anterior abdominal wall or anterior thigh, with vertical insertion of a 25G (orange hub) needle.

Table 4.6
Main concerns about drugs and health care products for certain groups of patients*

Groups	Main concerns
Buddhist	Animal and genetically modified (GM) products
Christian	Use of healthcare products and consumables produced through exploitation of disadvantaged people. Animal products, if production has involved cruelty to animals or animal research
Catholic	GM derivatives and those developed by fetal experimentation
Jehovah's witnesses	Not able to accept food and products that may contain blood or blood derivatives
Hindu	Gelatin-containing products, animal products and alcohol
Jain	Strict vegetarians, but will not eat root vegetables. Some patients, particularly those who follow vegan or vegetarian diets, may object to the use of animals to meet the needs of humans.
Muslims	Porcine and bovine derivatives, alcohol, non-Halal animal derivatives, E numbers derived from porcine products, and emulsifiers derived from animals
Jews	Products derived not only from pork, but also from any animal that had not been slaughtered according to Jewish law (Kosher). Devout Jews may wish to avoid alcohol
Sikhs	Beef and its derivatives

*From Scully C, Wilson N 2005 Culturally sensitive oral healthcare. Quintessence Publications

Intramuscular injection

This is used to obtain a more rapid effect than a subcutaneous injection, or where intravenous injection is impractical or carries a greater risk of anaphylactic or cardiac stimulant reaction. A 23G (blue hub) needle is used. Intramuscular (i.m.) injection is used for:

- epinephrine (adrenaline) in the emergency treatment of anaphylactic shock or cardiac arrest
- glucagon, in the emergency treatment of hypoglycaemia
- antipsychotics (e.g. chlorpromazine, haloperidol) in the emergency treatment of acute psychoses
- Midazolam or diazepam in the management of epileptic fit.
- antimicrobials.

Adverse effects of intramuscular injections include the following:

- Pain
- Bruising, due to local haematoma formation. Intramuscular injections are contraindicated in patients with bleeding tendencies (e.g. haemophilia or induced by anticoagulant therapy)
- Nerve damage, which may lead to paralysis, especially in bleeding disorders. This risk is minimized by using either the side of the thigh, or the upper, outer quadrant of the gluteus maximus muscle in the buttock or the deltoid muscle in the upper, outer arm
- Collapse, usually due to a faint
- Anaphylactic shock, especially after injections with antimicrobials, such as penicillins.

Intravenous injection

Intravenous (i.v.) injection is used to achieve a rapid effect in emergencies, for example:

- epinephrine (adrenaline) in the management of cardiac arrest only
- diazepam in the management of status epilepticus
- heparin in the management of acute pulmonary embolism.

I.V. infusion through an indwelling catheter is used:

- when administration by other routes is not possible (e.g. blood transfusion, or fresh frozen plasma or coagulation factor concentrates)
- for hydration with intravenous fluids (e.g. saline or dextrose) when oral intake of fluids is not possible (e.g. unconsciousness or semiconsciousness, impaired swallowing (e.g. after stroke), vomiting, or fasting prior to surgery or other procedures)
- for antimicrobial treatment of severe infections or infective endocarditis prophylaxis when using, for example, vancomycin.

Veins preferred for i.v. injections are those in the antecubital fossa, the preferred sites for infusions are the forearm or dorsal hand veins (which allow joint mobility). Note that:

- following insertion of the needle [usually 21G (green hub) or 23G (blue hub)] or catheter, the fact that the needle is in a vein and not elsewhere should be

confirmed by aspiration of blood and by the absence of local pain or swelling on injection or infusion of a small amount of the material to be administered

- intravenous catheters should be taped in place, and sterile precautions (and rotation of catheter sites) observed to minimize the risk of local thrombosis and sepsis
- when prolonged IV access is required (e.g. in treatment of endocarditis or malnutrition), a central venous catheter can be inserted (under full sterile conditions) into the internal jugular or subclavian veins. Such Hickman lines (central catheters) are also useful in monitoring central venous pressure and fluid replacement in circulatory shock
- after any injections, anaphylactic shock may occur, especially with antimicrobials, such as penicillins. The patient should be observed for 30 minutes, with facilities for resuscitation available.

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5

Agents used in the treatment of patients with oral disease

First do no harm.

Hippocrates

Introduction

Attention should first be directed to relieving pain, discomfort and anxiety. Many oral mucosal conditions can only resolve and be controlled with immunomodulatory therapy. Where specific therapies are available they should be used: for other conditions, the best that can be offered is symptomatic treatment – the control of symptoms (Chapter 4).

Analgesics

Pain is the most important symptom suggestive of oral disease, but absence of pain does not exclude disease. There is considerable individual variation in response to pain, and the threshold is lowered by tiredness and psychogenic and other factors.

It is important, therefore, where possible, to:

- identify and treat the cause of pain
- relieve factors that lower the pain threshold (fatigue, anxiety and depression)
- try simple oral analgesics initially, before embarking on more potent or injectable preparations or opioids
- Avoid polypharmacy.

Systemic analgesics (Table 5.1) can reduce pain, in some cases, such as non-steroidal anti-inflammatory drugs (NSAIDs), through an eicosanoid-depressing, anti-inflammatory action. The term 'eicosanoids' is used as a collective name for molecules derived from 20-carbon fatty acids – mainly the leukotrienes and prostanoids.

Leukotrienes play an important role in inflammation, especially as part of the Slow Reacting Substance of Anaphylaxis.

Prostanoids (prostaglandins, prostacyclin, thromboxanes) mediate local symptoms of inflammation: vasoconstriction or vasodilatation, coagulation, pain and fever. All prostanoids originate from prostaglandin H catalyzed by the enzyme PGH2-synthase, which is a combination of a peroxidase and a cyclo-oxygenase (COX) (Fig. 5.1).

Most NSAIDs act as non-selective inhibitors of COX, inhibiting both the isoenzymes COX-1 and COX-2. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from cellular phospholipase A₂). Prostaglandins stimulate protective gastric mucin and bicarbonate but reduce gastric acid; renal excretion and blood platelet formation. Prostaglandins released via COX-2 act (among other things) as messenger molecules in inflammation.

NSAIDs, including aspirin, are useful analgesics, but can:

- cause peptic ulceration, especially in those over 75 years old or who have a history of peptic ulceration. Thus it is best to add a proton pump inhibitor, such as misoprostol. Ibuprofen appears to be the conventional NSAID with the lowest risk of gastrointestinal adverse effects. COX-2 inhibitors, such as celecoxib, etoricoxib, valdecoxib and parecoxib, have fewer gastrointestinal effects, but may have cardiac adverse effects
- cause further deterioration of renal function, if this is already impaired
- produce a bleeding tendency, by interfering with platelet activity
- in pregnancy third trimester, cause premature closure of the ductus arteriosus.

Aspirin has been in use longer than most NSAIDs, and the efficacy and adverse effects are well recognized. Aspirin is useful but it can also:

- to cause bleeding irreversibly block the formation of thromboxane A₂ in platelets
- worsen asthma
- cause fluid retention
- cause nausea, diarrhoea or tinnitus
- increase methotrexate toxicity
- interfere with a number of drugs, including antihypertensives and diuretics
- cause allergies
- cause Reye syndrome – a serious liver disease, in children under age 16 years
- cause complications in mothers in late pregnancy
- in breast-feeding, pass in milk to the child and may cause Reye syndrome.

Paracetamol/acetaminophen inhibits COX, and is sometimes grouped together with the NSAIDs, but it is not a true NSAID and lacks significant anti-inflammatory properties and adverse effects of NSAIDs. There is

Table 5.1
Some analgesics

Agent	Adult dosage	Contraindications
Non-steroidal anti-inflammatory drugs (NSAIDs)		
Ibuprofen	400mg up to 4 times daily	Asthma, peptic ulcer, bleeding tendency, breast-feeding, cardiac renal and liver disease, pregnancy, elderly, aspirin hypersensitivity
Mefenamic acid	250–500mg up to 3 times daily	
Celecoxib	100mg twice daily	
Non-NSAIDs		
Paracetamol (acetaminophen)	500–1000mg up to 6 times daily (max. 4mg/day)	Liver or renal disease; those on zidovudine
Nefopam	30–60mg up to 3 times daily	Convulsive disorders, pregnancy, elderly, renal, liver disease
Opioids		
Codeine phosphate	10–60mg up to 6 times daily orally (or 30mg i.m.)	Liver disease, late pregnancy
Dihydrocodeine	30mg up to 4 times daily (or 50mg i.m.)	Children, hypothyroidism, asthma, renal disease, pregnancy, children, hypertension, respiratory depression, head injuries or raised intracranial pressure
Pentazocine	25–50mg up to 4 times daily (or 30mg i.m. or i.v.)	
Dextromoramide	5mg and 10mg tablets	Patients with head injury (since it interferes with pupillary responses and suppresses respiration), liver disease, kidney disease, pregnancy, breast-feeding, taking monoamine oxidase inhibitors
Methadone	5mg tablets	The elderly or debilitated patient, since accumulation occurs
Oxycodone	5mg capsules	Patients with head injury (interfere with pupillary responses and suppress respiration), liver disease, kidney disease, pregnancy, breast-feeding, taking monoamine oxidase inhibitors
Pethidine	50–100mg i.m. or 5–10mg s.c. or i.m.	
Fentanyl	100–200mg i.v. or i.m.	

speculation that it acts through the inhibition of COX-3 isoform, or that it acts centrally. Chronic pain requires regular analgesia (not just as 'required') and it is important not to overdose with paracetamol (acetaminophen) – which is hepatotoxic in high doses. In children can helpfully be given in sugar-free syrups.

- Anticonvulsants may control neuralgia
- Capsaicin, an alkaloid derived from peppers and used systemically or topically can, by depleting substance P in sensory nerve endings, and by blocking conduction in type-C nociceptive fibres, be helpful in post-herpetic neuralgia and oral dysaesthesia.

Topical analgesics and a variety of over-the-counter topical preparations are available to treat 'mouth ulcers', but few have been proved effective in controlled trials.

Opioids and narcotics

- Opioids are narcotics. They are controlled drugs and are all capable of causing addiction.
- Opioids are analgesics used for moderate to severe pain.
- Opioids may also cause constipation, respiratory depression, nausea, drowsiness and urinary retention.

Non-analgesic agents may be effective, for example,

- Antidepressants may control neuropathic pain. Tricyclics with balanced effects on serotonin and noradrenaline re-uptake (e.g. amitriptyline, nortriptyline) may be more effective than those acting mainly on noradrenaline uptake (e.g. maprotiline)

CNS-active drugs

Hypnotics

- Pain, anxiety or depression may cause insomnia.
- Hypnotics may help sleep, but should not be prescribed without forethought.
- Benzodiazepines such as temazepam 10mg nocte are, in general, the preferred hypnotics, but are

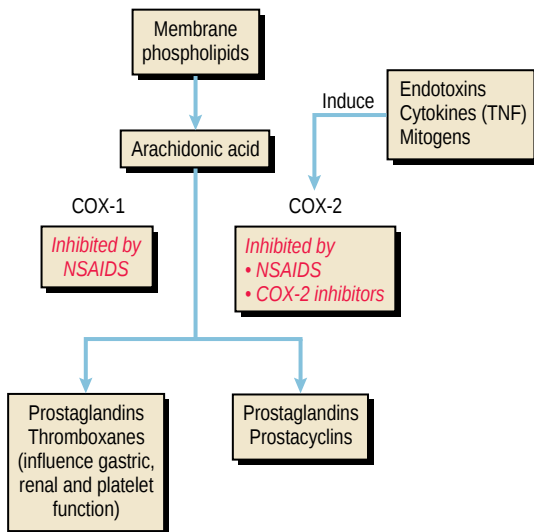


Fig. 5.1 COX

contraindicated in severe respiratory disorders and are also addictive.

- Barbiturates and glutethimide should not be used; both are dangerous in overdose and barbiturates are addictive.
- Hypnotics often potentiate alcohol and other CNS depressants, and may impair judgement and dexterity.
- Hypnotics may be contraindicated in the elderly and in those with liver or respiratory disease.

Anxiolytics

- Identify and treat the cause of the patient's anxiety wherever possible.
- It is important to differentiate between agitated depression and simple anxiety; the treatment is different.
- Reassurance is often remarkably effective at calming the anxious patient but there are times when a mild anxiolytic, such as a benzodiazepine like diazepam 1–10mg, or a non-benzodiazepine, such as buspirone 5mg orally three times daily, can be helpful.
- Numerous benzodiazepines are now available as anxiolytics. All may produce dependence (especially lorazepam) and there is often little to choose in terms of anxiolytic effect between the different drugs. Most (5-hydroxytryptamine: 5-HT) cause unsteadiness and some confusion.
- Buspirone (Table 5.2) probably acts by an effect on brain serotonin receptors and is not sedative. Buspirone may take up to 4 weeks at full dosage to have effect. Buspirone can interact with some antimicrobials, e.g. erythromycin, itraconazole and rifampicin, and should not be taken with MAOI antidepressants.

- Beta blockers (e.g. propranolol) may be more useful if anxiety is causing tremor/palpitations.
- Drowsiness (particularly when used together with alcohol) and impaired judgement are common in patients taking anxiolytics, so patients must be warned of the dangers of driving, operating machinery or making important decisions.
- Doses of anxiolytics should be reduced for the elderly, since adverse effects, particularly sedation, are common.

Antidepressants

Psychotherapy, drugs and possibly physical treatment are used for the treatment of depression. If there is any possibility of a suicide attempt the patient must be seen by a psychiatrist as a matter of urgency.

Antidepressants (Table 5.3) can also be useful for the relief of some neuropathic pain, when they can have analgesic effect within 1–7 days (before they have any antidepressant effect) and at lower doses than needed for treatment of depression.

Antidepressants:

- must be prescribed only in limited amounts, as there is a danger they may be used in a suicide attempt
- may take up to 2–4 weeks before the antidepressant action takes place. Monitoring of plasma concentrations may be helpful in ensuring optimal dosage
- doses should be reduced for the elderly patient
- should not be withdrawn prematurely. The natural history of depression is of remission after 3–12 months
- are usually contraindicated in patients with cardiac or liver disease
- may have adverse effects. Antidepressants often have anticholinergic activity and thus cause:
 - dry mouth, but the complaint of dry mouth may also be a manifestation of depression
 - epileptogenic effects (tricyclics and fluoxetine)
 - drowsiness
 - visual impairment
 - constipation and urinary retention
- make it impossible for patients taking them to drive vehicles, as they may suffer drowsiness and visual impairment
- may interact with other drugs as follows:
 - tricyclic antidepressants interact with norepinephrine (noradrenaline)
 - other antidepressant interactions include those with alcohol, antiarrhythmics, antiepileptics, antihistamines, antihypertensives, antipsychotics, apraclo-nidine, beta blockers, brimonidine, diuretics, the contraceptive pill, nefopam and tramadol.

Table 5.2
Anxiolytics

Drug	Dose	Comments
Buspirone	5mg 2–3 times daily	Avoid in epilepsy, liver disease, pregnancy, breast-feeding
Diazepam Temazepam	2–30mg/day in divided doses 5–10mg at night	Avoid in glaucoma. Use with caution in the elderly

Table 5.3
Some antidepressants

Drug	Dose	Comments
Amitriptyline Clomipramine Doxepin (dothiepin) Doxepin	25–75mg/day in divided doses 25mg 3 times daily or 75mg at night 25mg 3 times daily or 75mg at night 10–100mg/day in divided doses	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Fluoxetine	20mg/day	Caution with: epilepsy; pregnancy; cardiac, liver or kidney disease; allergy; mania
Nortriptyline	75–100mg/day	Contraindications: recent myocardial infarction, arrhythmias, liver disease
Venlafaxine	75mg in morning	Contraindications: recent myocardial infarction, arrhythmias, liver disease

Table 5.4
Drugs for treatment of trigeminal neuralgia*

Drug	Dose	Comments
Baclofen	5mg three times daily	Common adverse effect of sedation. Contraindicated in peptic ulceration and pregnancy. Avoid abrupt withdrawal.
Carbamazepine	Initially 100mg once or twice daily. Many patients need about 200mg 8-hourly. Do not exceed 1800mg daily.	Prophylactic for trigeminal neuralgia – not analgesic. Occasional dizziness, diplopia, and blood dyscrasia, often with a rash and usually in the first 3 months of treatment. Potentiated by cimetidine, dextropropoxyphene and isoniazid. Potentiates lithium, interferes with contraceptive pill. Contraindicated in cardiac, renal and liver disease, glaucoma and pregnancy.
Gabapentin	300mg up to three times daily	Similar adverse effects to carbamazepine. Headache common. Contraindicated in psychiatric disease, renal disease, diabetes and pregnancy. Avoid sudden withdrawal.
Phenytoin	150–300mg daily	Similar adverse effects to carbamazepine. Contraindicated in liver disease and pregnancy. Produces gingival swelling
Topiramate	25mg daily	Contraindicated in glaucoma and breast-feeding

*All may cause drowsiness and impair driving and skilled tasks

However, neither tricyclic antidepressants (TCAs) nor monoamine oxidase inhibitors (MAOIs) do not significantly interact with adrenaline in dental local anaesthetic solutions

Anticonvulsants

Anticonvulsants are used for the treatment of idiopathic trigeminal neuralgia (Table 5.4); carbamazepine is the standard treatment, but phenytoin or other agents may also be required if the pain is not controlled. As either

Table 5.5
Examples of topical corticosteroids

Steroid	Dosage every 6 hours	Comments
Hydrocortisone hemisuccinate pellets	2.5mg, dissolve in mouth close to ulcers	Use at an early stage of ulceration in recurrent aphthous stomatitis
<i>Medium potency</i>		
Betamethasone soluble phosphate tablets	0.5mg, use as mouthwash	Adrenal suppression possible
Betamethasone valerate 0.1% cream	Apply to lesion	
Flucinolone 0.025% cream	Apply to lesion	
Mometasone furoate 0.1% cream	Apply to lesion	
Triamcinolone acetonide 0.1% in carmellose gelatin paste	Apply to lesion	Adrenal suppression possible. Adheres best to dry mucosa; affords mechanical protection; of little benefit on tongue or palate.
<i>High potency</i>		
Beclomethasone (Beclomethasone) dipropionate spray	1 puff, 100ml	Adrenal suppression possible
Budesonide spray	1 puff, 100ml	
Desoximetasone	Apply to lesion	
Fluocinonide 0.05% cream, gel or ointment	Apply to lesion	
Fluticasone propionate spray or 0.05% cream	Apply to lesion	
Halcinonide 0.01% cream	Apply to lesion	
<i>Super potency</i>		
Betamethasone dipropionate 0.05% cream	Apply to lesion	Adrenal suppression possible
Clobetasol propionate 0.05% cream	Apply to lesion	
Halobetasol propionate 0.05% cream	Apply to lesion	
Prednisolone mouthwash	5mg	

may cause blood dyscrasias or hepatic dysfunction, it may be helpful to monitor full blood counts and liver function (see Chapter 38).

Immunomodulatory agents

Adverse effects are important mainly with systemic immunomodulatory agents and thus the preference is usually for topical agents, mainly the corticosteroids.

Corticosteroids

Glucocorticoids are the corticosteroids used for immunosuppression. Corticosteroids have a wide range of effects, including to inhibit:

- the transcription of immune genes such as interleukin-2 (IL-2) gene. IL-2 is the main cytokine necessary for the development of T cell immunologic memory (which depends upon the expansion of antigen-selected T cell clones)

- IL-1, IL-3, IL-4, IL-5, IL-6 and IL-8
- TNF- α
- eicosanoid production and prostaglandins and leukotrienes (via COX inhibition)
- via lipocortin-1, the emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators (lysosomal enzymes, cytokines, tissue plasminogen activator, chemokines, etc.) from neutrophils, macrophages and mast cells.

Topical corticosteroids

Topical corticosteroids (Tables 5.5 and 5.6) are useful in the management of many oral ulcerative conditions where there is no systemic involvement, such as recurrent aphthous stomatitis and oral lichen planus (Fig. 5.2):

- These steroids are used locally on a lesion as a spray, gel or cream, or as a mouthwash if there are extensive lesions.
- Creams, gels and sprays are better than ointments, since the latter adhere poorly to the mucosa. However, creams can be bitter and gels can irritate.

Table 5.6
Suggested topical corticosteroid creams

Medium potency	High potency	Super potency
0.1% triamcinolone acetonide; Adcortyl cream	0.5% fluocinonide; Metosyn cream	0.5% clobetasol propionate; Dermovate cream
0.025% fluocinolone acetonide; Synalar cream or gel	0.25% desoximetasone; Stiedex cream	0.05% betamethasone dipropionate; Diprosone cream
0.05% betamethasone valerate; Betnovate cream	0.1% halcinonide; Halciderm topical cream	—
0.05% fluticasone propionate; Cutivate cream	—	—



Fig. 5.2 Triamcinolone in Orabase

- The steroid needs to be in contact with the mucosa for some minutes for it to have any significant effect; patients should, therefore, time its use for at least 3 minutes on each occasion.
- Patients should not eat or drink for 30 minutes after using the steroid, in order to prolong contact with the lesion.
- The steroid can usefully be applied in a plastic splint worn overnight for treatment of desquamative gingivitis.
- With many topical steroids there is little systemic absorption and thus no significant adrenocortical suppression. In patients using potent steroids for more than a month it is prudent to add an antifungal, since candidiasis may arise.

Drawbacks of the steroids are that:

- there are few randomized controlled trials (RCTs)
- they are not uniformly effective
- occasionally candidiasis is a complication
- they can damage collagen
- there is no evidence on possible oncogenicity
- they are often not licensed for use in the mouth.

Topical calcineurin inhibitors

These include (Table 5.7):

- Ciclosporin
- Tacrolimus (Fig 5.3)
- Pimecrolimus.

Calcineurin inhibitors act by binding to immunophilins (cyclophilin and macrophilin) and these complexes inhibit calcineurin, which under normal circumstances induces the transcription of IL-2. Topical ciclosporin or tacrolimus can be:

- effective in ulcerative disorders
- more effective if used along with topical corticosteroids
- expensive.

Tacrolimus is:

- available as 0.1 and 0.03% creams
- liable to cause stinging for ~15 minutes (decreases on continued use)
- not licensed for use in mouth
- only rarely, associated with adverse effects. However, the US Food and Drug Administration (FDA) in 2005, issued a public health advisory warning about possible carcinogenicity.

Intralesional corticosteroids

These are occasionally useful in the management of intractable local lesions, such as erosive lichen planus and orofacial granulomatosis. Intra-articular corticosteroids are occasionally indicated where there is intractable pain from a non-infective arthropathy. Some examples include:

- prednisolone sodium phosphate, up to 22mg
- methylprednisolone acetate, 4–80mg
- triamcinolone acetonide, 2–3mg
- triamcinolone hexacetonide, up to 5mg.

Table 5.7
Alternative topical immunosuppressants (calcineurin inhibitors)

Drug	Dose	Comments
Ciclosporin (Neoral or Sandimmun), used as mouthwashes or in an adhesive medium Orabase-like preparation	100–1500mg/ml daily as a mouthwash; <50mg/ml daily in an adhesive preparation	Adverse effects rare with topical applications
Tacrolimus (Protopic or Prograf)	0.1–0.03% ointment	Adverse effects rare with topical applications. Has 10- to 100-fold potency of ciclosporin

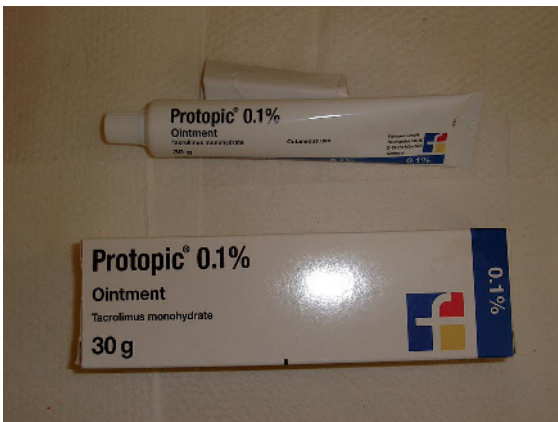


Fig. 5.3 Tacrolimus cream

- giant cell arteritis
- pemphigus
- severe or resistant oral ulceration in vesiculobullous conditions
- multisystem diseases, such as lichen planus, erythema multiforme or pemphigoid with oral, genital and cutaneous involvement.

Adverse effects

Systemic corticosteroids must always be used with caution because of potential adverse effects, which may include, apart from those noted above:

- Adrenocortical suppression. This may occur after a course of more than 3 weeks of systemic steroids and may persist for 1 year or more. Adrenocortical suppression makes the patient liable to collapse if stressed, traumatized or having an infection, operation or general anaesthetic.
- Weight gain and mooning of the face. Weight should be monitored. A diet low in salt, fats and calories helps control weight and prevent hypertension.
- Hypertension. The blood pressure must always be monitored.
- Precipitation of diabetes. The blood glucose must always be monitored.
- Cataract. Ophthalmological monitoring is indicated.
- Osteoporosis. Patients on protracted courses should have bone densitometry monitoring and be given bisphosphonates and calcium.
- Avascular necrosis of the femoral head.
- Psychoses.

Alternate-day administration after breakfast reduces the adverse effects of steroids (Table 5.9). Patients should always be given a steroid card, warned of possible adverse reactions, and warned of the need for an increase in the dose if ill or traumatized, or having an operation.

Systemic immunosuppressants

Systemic immunosuppressants (Table 5.8) include the following:

- Corticosteroids
- Azathioprine
- Cyclophosphamide
- Mycophenolate mofetil
- Leflunomide
- Methotrexate.

Adverse effects can be serious and include the following:

- Infections, especially with viruses, fungi and mycobacteria, such as tuberculosis
- Lymphoproliferative disorders
- Malignancies, such as lip carcinoma
- Teratogenicity.

Systemic corticosteroids

Indications

Systemic corticosteroids are often indicated for the management of:

- Bell's palsy

Steroid-sparing immunosuppressants

Because of possible adverse reactions of steroids, drugs with alternative modes of action are used as alternatives or in combination with steroids. However, most of these

Table 5.8
Systemic immunomodulatory agents*

Agent	Dosage	Possible side-effects and contraindications
Azathioprine	2–2.5mg/kg daily (50–150mg/day)	May take 2–3 months to have real effect. May cause bone marrow suppression, so thiopurine methyl transferase (TPMT) levels should first be assayed to detect genetic polymorphisms at risk (1:300). May also cause liver dysfunction, arrhythmias, hypotension, nephritis. Contraindicated in pregnancy. Small risk of cancer with prolonged use. Interactions: allopurinol (increases the effect of azathioprine), aspirin (bleeding), other immunosuppressants (increase the risk of infection)
Ciclosporin (cyclosporin)	1–2mg/kg daily	Nephrotoxic, hepatotoxic. May cause hypertension, blood dyscrasias, gingival swelling. Contraindicated in kidney disease, pregnancy, porphyria. Interactions: allopurinol, analgesics and antifungals (increase ciclosporin toxicity), anticonvulsants (reduced efficiency)
Colchicine	500mg 3 times daily	May cause diarrhoea and bone marrow suppression. Contraindicated in pregnancy, elderly, cardiac, renal or hepatic disease
Cyclophosphamide	1–2mg/kg daily	Can cause bone marrow suppression, cystitis. Small risk of cancer with prolonged use
Dapsone	1mg/kg daily (usually 100–200mg). Give also vitamin E 800IU/day, and cimetidine	Interactions: trimethoprim and methotrexate (increase the risk of haematological complications). See text p. 57
Hydroxychloroquine	200–400mg/day	May take 3–6 months to have effect. May cause retinal damage and visual impairment. May cause bone marrow suppression. Contraindicated in patients with renal or hepatic disease
Levamisole	50mg 3 times daily for 3 days	Promotes leucocyte chemotaxis. May cause dizziness, taste disturbance, nausea, agranulocytosis
Mycophenolate mofetil	1g twice daily	May take 2–3 months to have real effect. Used in transplants mainly. May cause bone marrow suppression and gastrointestinal effects. Contraindicated in pregnancy
Pentoxifylline	400mg twice daily	Contraindicated in cerebrovascular haemorrhage, myocardial infarction
Prednisolone (give as enteric coated prednisolone with meals)	Initially 30–80mg orally each day in divided doses, reducing as soon as possible to 10mg/day	May produce adrenal suppression. Limit dosage in hypertension and diabetes mellitus. May cause weight gain, osteoporosis
Tacrolimus	100mg/kg daily	Used in transplants mainly. May cause cardiomyopathy. Contraindicated in pregnancy
Thalidomide	50–200mg/day at night initially, then alternate-day therapy	May take 2–3 months to have real effect. Causes drowsiness in up to 50%. Teratogenic. Neurotoxic; may cause axonal neuropathy, so take sensory nerve action potential (SNAP) records in sural and median nerves every 6 months. This is dose-related, and in 50% is irreversible: most neuropathy has occurred in patients taking 100mg/day or more for 6 months or longer. Other effects include constipation, rash, oedema and reversible lymphopenia

*Many can increase liability to infection and, long term, possibly also neoplasia.

Table 5.9
Reducing course of systemic corticosteroid

Short-course treatment schedule: 105 prednisolone 5 mg tablets to cover an almost 4-week period												
Day	1	3	5	7	9	11	13	15	17	19	21	23
No. of tablets to take after breakfast	12	12	12	9	9	9	9	6	6	6	6	3
Steroid dose in mg over 2 days	60	60	60	45	45	45	45	30	30	30	30	15

Patient information sheet

CORTICOSTEROID TREATMENT (THIS SHEET IS FOR SYSTEMIC STEROIDS ONLY)

Please read this information sheet. If you have any questions, particularly about the treatment of potential side-effects, please ask your doctor.

- Corticosteroids are very helpful, but must be used with caution.
- Always tell an attending doctor or dentist you are on steroids.
- Always carry your steroid card.
- The steroid dose must usually be increased if you:
 - are ill
 - have an accident
 - have an operation.
- Adverse effects seen on treatment for over 4 weeks can include:
 - weight gain and fat re-distribution
 - hypertension (high blood pressure)
 - precipitation of diabetes
 - osteoporosis
 - mood changes
 - liability to fungal and viral infection
- Alternate-day dosing reduces the adverse effects of steroids.

Adverse effects include the following:

- Haematological:
 - haemolysis
 - methaemoglobinaemia
 - agranulocytosis
- Liver dysfunction
- Renal dysfunction
- Hypersensitivity
- Headaches
- Photosensitivity.

Contraindications include the following:

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Methaemoglobin reductase deficiency
- Anaemia
- Porphyria
- Liver disease
- Pregnancy and breast-feeding
- Allergies to:
 - dapsone
 - naphthalene
 - niridazole
 - nitrofurantoin
 - phenylhydrazine
 - sulfa drugs
 - primaquine.

Baseline observations should include:

- Full (complete) blood count
- Reticulocyte count
- Haptoglobin level
- G6PD level
- Liver function
- Renal function.

Treatment regimen:

- Ensure no G6PD deficiency
- Dapsone 25mg/day for 3 months
- Cimetidine (400mg) and vitamin E (800U) to minimize haemolysis (inhibit conversion of dapsone to its toxic hydroxylamine)
- Clothing, sunglasses, and sunscreen to avoid sun.

drugs may have serious, adverse effects in addition to those noted above, and so they are used by specialists and, indeed, are not widely used in oral medicine practice. These steroid-sparing drugs include dapsone, azathioprine, cyclophosphamide, mycophenolate mofetil, leflunomide, colchicine, thalidomide, pentoxifylline and ciclosporin. Of these, dapsone is most widely used and, therefore, most fully described.

Dapsone

- Antioxidant
- Interferes with neutrophil functions (adherence, chemotaxis, prostaglandin E2 release, lysosomal enzyme release, myeloperoxidase-hydrogen peroxide-halide mediated cytotoxicity)
- Overall:
 - efficacy ~60%
 - adverse effects ~25%.

Monitor:

- Blood: weekly for month 1, then alternate weeks during the next 2 months, and every 3 months thereafter
- Methaemoglobin levels in patients who become symptomatic for methaemoglobinaemia
- Liver and renal function every 3 months
- For drug hypersensitivity over first 5 weeks.

Azathioprine

- A 6-mercaptopurine pro-drug, which blocks nucleotides and DNA
- Assay TPMT (thio-purine methyl transferase) first
- Bone marrow suppression in low TPMT
- Takes 4–8 weeks for effect.

Cyclophosphamide

- Transformed by cytochrome p450 to active phosphoramidate mustard and acrolein, which reacts with DNA
- Leukopenia always – but reversible
- Macrocytosis.

Mycophenolate mofetil

- Inhibits inosine monophosphate dehydrogenase (blocks guanosine nucleotide, purine and DNA synthesis) and thereby blocks T and B cell proliferation and leukocyte recruitment
- No liver or kidney damage
- More gastrointestinal, haematological effects and infections than with azathioprine.

Leflunomide

- A prodrug, completely converted to its active metabolite A 77 1726 (M1) which blocks dihydro-orotate dehydrogenase, a key enzyme of pyrimidine synthesis
- Teratogenic in both genders
- Hepatotoxic (never use with methotrexate)
- Myelotoxic.

Ciclosporin

Adverse effects of systemic ciclosporin are shown in Table 5.8.

Colchicine

Colchicine is a poisonous alkaloid, originally extracted from *Colchicum* (Autumn crocus – the ‘Meadow saffron’). Colchicine inhibits mitosis by binding to tubulin in microtubules, and thus depresses neutrophil motility and activity.

Adverse effects include the following:

- Gastrointestinal upset
- Neutropenia
- Bone marrow damage.

Anti-tumor necrosis factor alpha (TNF) agents

TNF- α induces the synthesis of IL-1 and IL-6 and the adhesion of lymphocyte activating molecules.

Thalidomide

Originally used in the 1950s as a sedative, Thalidomide was withdrawn in 1961 because of birth defects when given to pregnant women. Since then it has been found to benefit several severe conditions unresponsive to other treatments but related to tumour necrosis factor (TNF) release:

- Patients given thalidomide may need a pregnancy test to check this is negative before starting thalidomide treatment, must take effective contraceptive measures while taking thalidomide and for 3 months after finishing the tablets, and must not get pregnant.
- Nerve damage can occur during thalidomide treatment. Nerve conduction tests are needed before the start of treatment, and these should be repeated every 6 months. Nerve damage will recover on stopping the treatment in approximately 50% of cases, but in others may be permanent.
- Thalidomide makes most people feel drowsy. It should be taken at night. Drowsiness persisting during the day makes it unsafe for patients to drive or operate machinery, and may impair alertness and ability to think clearly. Alcohol must be avoided.

Pentoxifylline

Pentoxifylline is a xanthine derivative, a cyclic nucleotide phosphodiesterase inhibitor that also improves blood flow through blood vessels. The biological effects include inhibition of proinflammatory cytokine production, leukocyte–endothelial cell adhesion, chemokines and leukocyte–keratinocyte adhesion

Common adverse reactions are nausea, dysphagia, and flushing.

Monoclonal antibodies suppressing TNF- α or other cytokines

Monoclonals acting against TNF- α include infliximab (Remicade), etanercept (Enbrel), or adalimumab (Humira).

Drugs that act by binding the IL-2 α receptor's α chain, preventing the IL-2 induced clonal expansion of activated lymphocytes and shortening their survival are also attractive; they include basiliximab (Simulect) and daclizumab (Zenapax). These agents are not currently routinely used in oral medicine practice.

Tetracyclines

Tetracyclines can be anti-inflammatory via non-antimicrobial actions which include:

- Down-regulation of pro-inflammatory cytokines
- Inhibition of matrix metalloproteinases (MMPs), including collagenases:
 - MMP-1
 - MMP-8
 - MMP-13
- Inhibition of prostaglandin synthesis
- Inhibition of nitric oxide release
- Inhibition of caspase activation (by minocycline).

Adverse effects:

- Hyperpigmentation
- Gastrointestinal discomfort
- Nausea, anorexia
- Photosensitivity
- Hypersensitivity
- Lupoid reactions
- Serum sickness-type reaction.

Contraindications:

- Children
- Liver disease
- Lupus erythematosus
- Myasthenia gravis
- Porphyria.

Tetracycline absorption is inhibited by zinc, iron and antacids.

Retinoids

Tretinoin as a 0.1% cream or 0.01% gel, or acitretin (pro-drug of etretinate) 10–50mg/day orally, may be of value in controlling lichen planus. Systemic retinoids however, are teratogenic and may disturb liver function and blood lipids.

Antimicrobials

Antibacterial therapy

- The bacteria which cause most odontogenic infections are sensitive to penicillins.

- Anaerobes have now been implicated in many odontogenic infections, and these often respond to penicillins or metronidazole.
- Amoxicillin 500mg three times daily is effective, and produces high blood antimicrobial levels, with good patient compliance.
- Flucloxacillin 500mg four times daily is also effective against many oral bacterial infections.
- If the patient is allergic, has had penicillin within the previous month (resistant bacteria) or has meticillin-resistant *Staphylococcus aureus* (MRSA) a different antimicrobial should be used.
- Drainage must be established if there is pus; antimicrobials will not remove pus.
- A sample of pus (as much as possible) should be sent for culture and sensitivities, but, if antimicrobials are indicated, they should be started immediately and in adequate doses.
- If a lesion fails to respond to an antimicrobial reconsider possible:
 - inadequacy of drainage
 - inappropriateness of the antimicrobial
 - inadequate antimicrobial dose
 - antimicrobial insensitivity of causal micro-organism, e.g. staphylococci are now frequently resistant to penicillin and some show multiple resistances (e.g. MRSA) when vancomycin is usually effective
 - patient non-compliance
 - local factors (e.g. foreign body)
 - unusual type of infection
 - impaired host defences (unusual and opportunistic infections are increasingly identified, particularly in the immunocompromised patient)
- non-infective cause for the condition.

In serious, unusual or unresponsive cases of infection, consult the clinical microbiologist.

Indications for the use of antimicrobials

Infections (together with appropriate surgical or other measures), such as:

- cervical fascial space infections
- osteomyelitis
- odontogenic infections in ill or toxic patients (e.g. if the patient is immunocompromised)
- acute ulcerative gingivitis
- specific infections, such as tuberculosis and syphilis.

Antimicrobials should be used in some instances of surgical conditions if they do not respond to local measures:

- pericoronitis
- dental abscess
- dry socket.

Antimicrobials should be used for prophylaxis:

- of infective endocarditis in at-risk patients having invasive oral procedures
- in cerebrospinal rhinorrhoea
- in most facial or compound skull fractures
- in major oral, maxillofacial and craniofacial surgery (e.g. osteotomies or tumour resection)
- in surgery involving bone in immunocompromised or debilitated patients
- in surgery involving bone in patients who have been taking bisphosphonates
- in surgery involving bone following radiotherapy to the jaws
- possibly in patients with hydrocephalus shunts having invasive oral procedures
- possibly in some patients with prosthetic joint replacements having invasive oral procedures, especially following rheumatoid arthritis.

Using antimicrobials

- The practitioner should attempt to obtain relevant specimens before commencing therapy.
- For most infections, a 5-day course of antibiotics is adequate.
- Antibiotic prescriptions should be reviewed at 48 hours and 5 days, and in the light of microbiology results.
- Most infections should be treated with a single antibiotic only. Exceptions include endocarditis prophylaxis, tuberculosis treatment and some infections in immunocompromised persons.
- Always enquire first about allergies.

Antifungal therapy

Antifungals (Table 5.10) are used:

- to treat oral or oropharyngeal fungal infections, but underlying predisposing factors should be corrected first
- until there is no evidence of residual clinical lesions or symptoms, and should be continued for at least 2 weeks more, to reduce the risk of recurrence
- topically often effectively and, importantly, they are without serious adverse effects apart from occasional drug interactions (e.g. topical miconazole can enhance the effect of warfarin)
- systemically and though sometimes more effective against *Candida*, systemic use can be associated with adverse effects or drug interactions.

Polyene antifungal agents

These are best and safely used topically for oral candidiasis in most instances, and include the following:

- Nystatin, which needs to be applied at least four times daily, 500 000 units for adults and 100 000 units for children (Fig. 5.4). Higher doses may be required in immunocompromised patients. Compliance can be a problem because of the taste, but pastilles or suspensions often overcome this disadvantage. Nystatin, if swallowed, may lead occasionally to gastrointestinal side-effects, such as nausea, vomiting and diarrhoea.
- Amphotericin, used as an oral suspension 100mg/mL, or lozenges 10mg, is an effective antifungal for oral candidiasis. It can be given intravenously for systemic candidiasis, but there is then a considerable risk of toxicity, which may manifest as fever, vomiting, and renal, bone marrow, cardiovascular and neurological toxicity. The most significant toxicity when used systemically is renal damage, which may develop in up to 80% of patients.
- Flucytosine (5-fluorocytosine) may be used as oral therapy for candidiasis in a dose of 50–150mg/kg/day, in divided doses, four times daily. Toxicity is due to metabolic effects on bone marrow cells, nausea, vomiting and hepatic dysfunction. In addition, flucytosine is poorly tolerated in HIV/AIDS, with approximately half of patients developing leukopenia, and slightly less developing thrombocytopenia. *Candida albicans* strain B may be resistant.

Azole agents

These include imidazoles (clotrimazole, miconazole, econazole and ketoconazole) and triazoles (fluconazole, itraconazole and voriconazole). Azoles are synthetic antifungals with broad-spectrum activity and are fungistatic, but are expensive and usually used mainly systemically, though miconazole in particular is often used topically.

Azoles inhibit the fungal cytochrome P450 dependent enzymes, which are essential catalysts for the 14-demethylation of lanosterol in sterol biosynthesis, and, therefore, block the synthesis of ergosterol, the principal sterol in fungal cell membranes. One adverse effect of azoles, therefore, is the accumulation of precursors of ergosterol. The imidazoles (ketoconazole and miconazole) have more effect on cytochromes than do the triazoles, and the latter thus tend to have less severe adverse effects. However, none of the azoles are entirely benign; hepatotoxicity may be common to all, and the potential for endocrine toxicities exists, particularly at high doses.

Another effect of azoles is on the metabolism of other drugs, such as ciclosporin, the dose of which should, therefore, be reduced, and there can be interactions with

Table 5.10
Antifungals

Agent	Dosage and duration (continue for at least 48 hours after lesions have cleared)*	Possible drug interactions and contraindications†
Chlorhexidine	0.12–0.2% mouth rinse twice daily	Tooth staining, especially if the patient drinks tea, coffee or red wine
Amphotericin	10mg lozenge, 100mg/ml suspension, 10–400mg 6-hourly for at least 14–21 days	Topical use – no problems
Amphotericin (i.v.)	0.5mg/kg for at least 10–14 days	Expensive. Nephrotoxicity, arrhythmias, neuropathies, anaphylactoid reactions. Avoid in pregnancy. Liposomal amphotericin may be safer
Nystatin (topical)	500 000IU lozenge, 100 000IU pastille, 100 000IU per ml of suspension. 100 000IU 6 hourly for at least 14–21 days. Suspension contains sucrose	Topical use often no problems but may be unpleasant taste, nausea or gastrointestinal disturbance
Clotrimazole (topical)	10mg 6-hourly for at least 14 days. Contains sucrose. Not available in the UK	Difficult to dissolve if mouth dry
Miconazole (topical)	250mg tablet, 25mg/ml gel. 250mg 6-hourly for at least 14–21 days 50mg/g denture lacquer; apply weekly for at least 2 weeks. Not available in the USA	May interact with many drugs, including antidiabetic drugs, anticoagulants, phenytoin, midazolam, ciclosporin, cisapride and terfenadine. Avoid in pregnancy, porphyria. May impair oral contraceptive. Even topical agent may be absorbed systemically
Ketoconazole (oral)	200–400mg/day for at least 14 days	May interact with many drugs, including anticoagulants, phenytoin, midazolam, ciclosporin, sertindole, terfenadine, cisapride, cimetidine and ranitidine (reduced absorption), isoniazid and rifampicin (reduce the effect of this drug), antidiabetic drugs (increase the effect of this drug). Enhances nephrotoxicity of ciclosporin. Avoid in pregnancy, porphyria. Hepatotoxic. Expensive. May impair oral contraceptive
Fluconazole (oral)	50–200mg/day for at least 14 days	May interact with many drugs, including antidiabetic drugs, anticoagulants, phenytoin, midazolam, ciclosporin, zidovudine, terfenadine, cisapride. Avoid in pregnancy, porphyria. May sometimes be hepatotoxic and myelosuppressive. Expensive. May impair oral contraceptive. Avoid in pregnancy, infants, renal disease. Less toxic than ketoconazole
Itraconazole (oral)	100–200mg/day for at least 14 days. 10mg/ml liquid 10ml twice daily for at least 14 days	May interact with many drugs, including digoxin, sertindole, anticoagulants, phenytoin, midazolam, ciclosporin, simvastatin, terfenadine, cisapride. Avoid in cardiac disease, pregnancy, porphyria. Expensive. May impair oral contraceptive
Voriconazole (oral)	200–400mg/day for at least 14 days	For fluconazole-resistant <i>C. albicans</i> or <i>C. krusei</i> infections. Contraindicated in cardiac disease, liver disease, pregnancy. May prolong QT interval. Avoid in breast feeding. Wide range of possible adverse effects. May cause nausea, neuropathy, rash. Interacts with terfenadine, cisapride and astemizole
Caspofungin	IV infusion 50mg daily	For fluconazole-resistant <i>C. albicans</i> . Contraindicated in cardiac disease, liver disease, pregnancy. Avoid in breast feeding. Wide range of possible adverse effects including anaphylaxis. Interacts with ciclosporin and tacrolimus.

*The higher doses are used in HIV infection

†Check pharmacopoeia for other contraindications, cautions and interactions



Fig. 5.4 Nystatin

antacids, sucralfate, phenobarbitone, isoniazid, phenytoin, rifampicin, terfenadine, H₂ receptor antagonists and warfarin. Rifampicin, rifabutin and phenytoin can decrease antifungal levels.

Finally, azole resistance is increasingly reported. The development of cross-resistance of *C. albicans* to different azoles during treatment with a single derivative has been described.

Azoles may thus:

- be hepatotoxic
- displace protein-bound drugs and, thus, enhance the activity of, for example, anticoagulants, producing a bleeding tendency
- interact with a number of drugs. An important interaction is to produce arrhythmias with terfenadine (and in the past with astemizole and cisapride). They may also interfere with the oral contraceptive
- cause antifungal resistance (to ketoconazole, fluconazole, miconazole and itraconazole) and this is now becoming a significant problem in immunocompromised persons, especially those with a severe immune defect, who may show *Candida* species resistant to fluconazole and, sometimes, to other azoles. Voriconazole may then be effective

Clotrimazole

Clotrimazole is used only topically as a 10mg troche three times daily, because it has gastrointestinal and neurological toxicity. It is less effective than other azoles in patients with HIV infection.

Ketoconazole

Ketoconazole may be used topically as a cream to treat angular stomatitis. Ketoconazole is usually used systemically, 200–400mg/day taken orally with food, since gastric acid is essential for its dissolution. Absorption

can be enhanced by taking orange juice, carbonated beverages or glutamic acid. Ketoconazole is poorly absorbed from an empty stomach in HIV/AIDS because of gastric atrophy and reduced acid production, or if there is concurrent use of medications, such as cimetidine, ranitidine and other antacids. It is also poorly absorbed if rifampicin or phenytoin are given. Adverse effects may include nausea, rashes, abdominal pain and pruritus, but especially liver damage. Transient disturbance of liver function (e.g. increased serum aminotransferase concentrations) is so common that regular monitoring with liver function tests is essential in all patients on systemic ketoconazole for more than a few days. Severe liver damage may sometimes occur. Ketoconazole also blocks hormone steroid synthesis and reduces testosterone levels. Adrenocortical suppression may also develop. Drug interactions with ketoconazole are shown in Table 5.10. These adverse effects have restricted its use.

Miconazole

Miconazole is used mainly for topical treatment of various forms of candidiasis, such as angular stomatitis. Miconazole lacquer is effective for the treatment of chronic atrophic candidiasis; chewing gum may be effective against intraoral candidiasis. Miconazole is also available for parenteral use against systemic mycoses, but the injection contains polyethoxylate castor oil, which may provoke allergic reactions. Intravenous miconazole may also cause liver damage and pruritus, nausea, blood dyscrasias, hyponatraemia, hyperlipidaemia and dysrhythmias.

Fluconazole

Fluconazole, like some other azoles, acts by inhibiting fungal ergosterol production, which is essential in cell wall formation, but it has little affinity for cytochromes, which is thought to explain its lower toxicity. Fluconazole is active against most *C. albicans*, though resistance may appear (see below) and it is less active against some non-*albicans Candida* species. It tends to be active against *C. parapsilosis* and *C. tropicalis*, but less active against *C. glabrata*, and is inactive against *C. krusei*. Fluconazole is well absorbed from the gut, even in the absence of gastric acidity, and absorption is rapid and nearly complete within 2 hours. Fluconazole appears to undergo relatively little metabolism in the body, elimination being predominantly renal with a half-life of approximately 30 hours, meaning that fluconazole can be given once daily, in a dose of 50–100mg. It also enters saliva. Fluconazole has generally been well tolerated, toxicity is mild and infrequent and, with usual doses, fluconazole does not appear to suppress the synthesis of corticosteroid hormones. Drug interactions present less difficulties than those associated with ketoconazole (see Table 5.10 and Ch. 6). An oral suspension of fluconazole is also available.

Itraconazole

Itraconazole is an orally active triazole that inhibits ergosterol biosynthesis in the fungal cell. It is available in 50mg and 100mg capsules and as a 10mg/ml oral solution. Itraconazole has a long half-life and fewer side-effects than ketoconazole, but is expensive, is eliminated hepatically and its use is contraindicated in liver disease. Itraconazole is well absorbed, but absorption is impaired when gastric acid is reduced or when antacids, rifampicin or phenytoin are given. Adverse effects of itraconazole have included altered liver function (but hepatotoxicity is less than that of ketoconazole) and hypokalaemia with hypertension due to accumulation of steroids with an aldosterone-like activity, mild leukopenia, nausea, epigastric pain, headache and oedema. Drug interactions are shown in Table 5.10.

Voriconazole

Voriconazole is a relatively new triazole antifungal agent, mainly indicated for the primary treatment of acute invasive aspergillosis. The primary mode of action is the inhibition of fungal cytochrome-P450-mediated 14- α -lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. Elevated liver function tests, cardiac QT interval, rash and visual disturbances are the main treatment-related adverse events.

Antiviral therapy

- Most antivirals (Table 5.11) achieve maximum benefit if given early in the disease.
- Most acute viral infections resolve naturally, though in immunocompromised persons they may be severe, widespread or persistent.
- Immunocompromised patients with viral infections may thus benefit from active antiviral therapy.
- Antiviral resistance is now becoming a significant problem to immunocompromised persons, especially those with a severe immune defect.
- Some antivirals active against herpesviruses and some active against retroviruses, such as HIV, are available, but there are few other antiviral agents of proven efficacy.

Antivirals active against herpesviruses

Nucleoside analogues

Nucleoside analogues compete with natural nucleosides to block virus DNA synthesis. Pro-drugs generally produce greater bioavailability of the active agent. Antivirals include the following:

- Aciclovir, a guanosine analogue selectively phosphorylated to active form by herpesvirus thymidine kinases (Figs 5.5 and 5.6). Aciclovir has a proven efficacy in herpes simplex virus (HSV) infections, including herpes labialis. It is not effective against cytomegalovirus (which has no such thymidine kinase).
- Valaciclovir is a pro-drug of aciclovir.
- Penciclovir is a relatively new synthetic acyclic guanine derivative which:
 - possesses the same antiviral spectrum as aciclovir
 - has a similar mechanism of action to that of aciclovir, in that it undergoes phosphorylation in response to HSV viral thymidine kinase and is then further phosphorylated by host cell enzymes into a triphosphate, which selectively inhibits HSV viral DNA replication
 - has considerably more bioavailability – up to 77% against the 10–20% for aciclovir
 - has a longer intracellular effect than aciclovir
 - is generally more effective clinically than aciclovir
 - is cheaper than aciclovir but only available as a cream
 - as a 1% cream applied every 2 hours for 4 days is effective treatment in herpes labialis.
- Ganciclovir, a guanosine analogue, is active against cytomegalovirus (CMV), but is more toxic than aciclovir, can produce neutropenia, may have carcinogenic activity and, if given with zidovudine, can produce profound myelosuppression.
- Cidofovir is a DNA polymerase chain inhibitor, active against cytomegalovirus and human papillomaviruses (HPV), but is nephrotoxic and may produce eye damage.
- Famciclovir, a guanosine analogue, is particularly useful against HSV and varicella-zoster virus (VZV), but produces DNA mutations that may predispose to (VZV) cancer of the breast or testis. Famciclovir is a pro-drug of penciclovir.

Other antiherpes agents

- Docosanol is an aliphatic alcohol that inhibits fusion between the plasma membrane and the HSV envelope, thereby preventing viral entry into cells and viral replication. A 10% docosanol cream is available for treating herpes labialis.
- Inosine pranobex (isoprinosine; methisoprinolol) is a stimulator of immunity via actions like thymic hormones, active against HSV and HPV. It should be used with caution in gout or renal disease.
- Foscarnet is an organic analogue of inorganic pyrophosphate that selectively inhibits the pyrophosphate binding site on viral DNA polymerases and can be used for HSV or CMV infections.

Table 5.11
Antivirals against herpesviruses

Virus	Disease	Otherwise healthy patient	Immunocompromised patient
HSV	Primary herpetic gingivostomatitis	Consider oral 100–200mg aciclovir tablets* 5 times daily, or oral suspension (200mg/5ml) 5 times daily	Consider aciclovir 250mg/m ² i.v. every 8 hours, or valaciclovir orally 1g bd, or famciclovir 500mg bd
	Recurrent herpes labialis	or valaciclovir orally 500mg bd or famciclovir 250mg three times daily 1% penciclovir cream every 2 hours or 5% aciclovir cream every 2 hours	Aciclovir 100–200mg tablets 5 times daily, or oral suspension (200mg/5ml) 5 times daily. Consider aciclovir 250mg/m ² i.v. every 8 hours.
	Recurrent herpetic ulcers	Aciclovir tablets* 5 times daily, or oral suspension (200mg/5ml) 5 times daily	Consider aciclovir 250mg/m ² i.v. every 8 hours.
VZV	Chickenpox*	—	Aciclovir 500mg/m ² (5mg/kg) i.v. every 8 hours or valaciclovir orally 1g tds
	Zoster (shingles)	3% aciclovir ophthalmic ointment for shingles of trigeminal ophthalmic division or famciclovir 250mg three times daily or valaciclovir 500mg bd	Famciclovir 500mg three times daily

*In neonate – treat as if immunocompromised.

Aciclovir (systemic preparations) and valaciclovir – caution in renal disease and pregnancy. Occasional increase in liver enzymes and urea, rashes, CNS effects.

Famciclovir – caution in renal disease and pregnancy. Occasionally causes nausea and headache.



Fig. 5.5 Aciclovir tablets



Fig. 5.6 Aciclovir ointment

Antiretroviral agents

Antiretroviral agents (Tables 5.12, 5.13 and 5.14) have been developed in the past decade, and though effective all are liable to fairly severe adverse reactions and resistance.

Nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs) block HIV reverse transcriptase activity by competing with natural substrates and being incorporated into viral DNA where they act as chain terminators in the synthesis of pro-viral nucleic acids. The NRTIs often produce adverse effects and, perhaps more significantly, HIV-resistance may arise. Among the common effects of many are haematological toxicity, neurological toxicity

(including effects on memory, cognition, motor and peripheral nerve function) and enhanced risk of oral infection, ulcers and erythema multiforme. They include (Table 5.12):

- abacavir
- didanosine (dideoxyinosine, DDI), which can also produce xerostomia
- emtricitabine
- lamivudine (3TC)
- stavudine (D4T)
- tenofovir
- zidovudine (ZDV) (azidothymidine, sometimes termed AZT), which can also produce hyperpigmentation.

Table 5.12
Antiretroviral drugs: nucleoside reverse transcriptase inhibitors (NRTIs)

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Abacavir ABC	Ziagen	Erythema multiforme	Lactic acidosis, nausea, diarrhoea, life-threatening rash
Didanosine DDI	Videx	Erythema multiforme, xerostomia	Nausea, diarrhoea, lactic acidosis, mitochondrial dysfunction leading to pancreatitis, abnormal liver function, peripheral neuropathy, retinal damage
Emtricitabine	Emtriva	–	Similar to lamivudine. Pruritus, hyperpigmentation
Lamivudine 3TC	Epivir	Xerostomia	Nausea, diarrhoea, mitochondrial dysfunction leading to pancreatitis, abnormal liver function
Stavudine D4T	Zerit	–	Neuropsychiatric reactions, mitochondrial dysfunction leading to pancreatitis, abnormal liver function
Tenofovir disoproxil	Viread	–	Renal tubular damage, hypophosphataemia
Zidovudine (azidothymidine) AZT ZDV	Retrovir	Erythema multiforme, hyperpigmentation	Nausea, diarrhoea, bone marrow suppression, lactic acidosis, myopathy

Table 5.13
Antiretroviral drugs: non-nucleoside reverse transcriptase inhibitors (NNRTIs); and others

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Efavirenz	Sustiva	Erythema multiforme	Interferes with liver drug-metabolizing enzymes, neuropsychiatric reactions
Nevirapine	Viramune	Erythema multiforme, ulcers	Induces liver drug-metabolizing enzymes, abnormal liver function
<i>Others</i>			
Enfuvirtide	Fuzeon	–	Hypersensitivity, pancreatitis, hypertriglyceridaemia

Non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) directly bind to HIV reverse transcriptase to inhibit it. NNRTIs suffer from similar disadvantages to NRTIs, especially rashes (Table 5.13).

Protease inhibitors

Protease inhibitors (PIs) competitively inhibit an HIV aspartyl protease without affecting the human enzyme, and they induce a profound and sustained fall in HIV viral load and restore T-cell counts. Drug-induced lipodystrophy may cause dyslipidaemia and facial

lipodystrophy. Taste abnormalities are common and oral and perioral paraesthesia can be disturbing adverse effects. Indinavir, which has activity related to vitamin A analogues, can also produce cheilitis. PIs include:

- amprenavir
- atazanavir
- fosamprenavir
- indinavir
- lopinavir
- nelfinavir

Table 5.14
Antiretroviral drugs: protease inhibitors

Proper name	Trade name	Possible orofacial adverse effects	Other main adverse effects
Amprenavir APV	Agenerase. Not licensed in the UK	Perioral paraesthesia, parotid lipomatosis	Interferes with liver drug-metabolizing enzymes, dyslipidaemia
Atazanavir	Reyataz	Ulcers	Prolongs QR interval, jaundice, neurological effects
Fosamprenavir	Telzir	Perioral paraesthesia, parotid lipomatosis	Interferes with liver drug-metabolizing enzymes, dyslipidaemia
Indinavir IDV	Crixivan	Cheilitis, parotid lipomatosis, xerostomia, taste disturbance	Nephrolithiasis in 40%, interferes with liver drug-metabolizing enzymes, oesophagitis, haemolysis
Nelfinavir NFV	Viracept	Parotid lipomatosis, xerostomia	Nausea, diarrhoea, interferes with liver drug-metabolizing enzymes, dyslipidaemia
Ritonavir RTV	Norvir	Perioral paraesthesia, parotid lipomatosis, xerostomia, taste disturbance, facial oedema	Nausea, diarrhoea, interferes with liver drug-metabolizing enzymes, flushing, dyslipidaemia
Saquinavir SQV	Fortovase, Invirase	Erythema multiforme, ulcers, parotid lipomatosis, xerostomia	Nausea, diarrhoea, interferes with liver drug-metabolizing enzymes, dyslipidaemia
Tipranavir	Aptivus	–	Hepatotoxicity and bleeding tendency

- ritonavir
- saquinavir
- tipranavir.

Combination therapy

Active antiretroviral therapies (ART), or highly active antiretroviral therapies (HAART) are combinations, involving a protease inhibitor and other antiretroviral drugs, which have reduced the incidence of opportunistic infections, extended life substantially and decreased the infective load of HIV and other viruses. Such has been the effect of ART and HAART, that the orofacial disease caused by HIV/AIDS, which was reduced by combination therapy, has now been significantly reduced by ART. Conversely, oral and perioral adverse

effects can arise and may sometimes result in patient non-adherence to anti-HIV therapy. Immune reconstitution syndrome is the term given when ART provokes an inflammatory reaction against residual micro-organisms.

CCRS entry inhibitors

Maraviroc (Celsentri) is a recently introduced antagonist to the CCR5 chemokine receptor, which shows considerable promise as an antiretroviral therapy.

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SECTION 2

COMMON COMPLAINTS

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6

Cervical lymphadenopathy

Key points

Main causes of cervical lymph node enlargement

- Infections:
 - oral or local in the drainage area
 - upper respiratory tract
 - systemic
- Malignant disease:
 - oral or in the drainage area
 - upper respiratory tract
 - lymphoreticular
- Others

Neck lumps

The tonsil is lymphoid tissue located between the pillars of the fauces, and there is similar material in the posterior aspect of the tongue (lingual tonsil) and the posterior wall of the pharynx (adenoids). These three areas form a ring of lymphoid tissue around the oropharynx (Waldeyer's ring).

A wide range of diseases may present with lesions in the neck (Fig. 6.1), but the most common complaint is of swelling and/or pain in the lymph nodes (Box 6.1). The dental surgeon can often detect serious disease through neck examination. Tenderness and swelling should be documented. Over a quarter of the lymph nodes in the body are connected with cervical lymph nodes situated in the head and the neck. It is not surprising then, that many diseases of the lymphoid tissue present primarily in this region. Lymph nodes that are tender may be



Fig. 6.1 Visible swelling in the submandibular triangle of the neck

inflammatory (lymphadenitis). Lymph nodes swollen from acute infections are usually tender, soft and discrete, while chronic infections give firm lymph nodes. Nodes that are increasing in size and are hard, or fixed to adjacent tissues may be malignant. Nodes that are enlarged and firm and matted or rubbery may be due to leukaemia. In the lymphomas particularly, the nodes may be rubbery, matted together and fixed to deeper structures. In the systemic infective disorders the nodes are usually firm, discrete, tender and mobile.

Both anterior and posterior cervical nodes should be examined as well as other nodes, liver and spleen if systemic disease is a possibility. Generalized lymphadenopathy with or without enlargement of other lymphoid tissue such as liver and spleen (hepatosplenomegaly) suggests a systemic cause.

Discrete swellings in the neck may occasionally be caused by disorders in:

- the salivary glands
- the thyroid gland
- other structures.

Box 6.1

More comprehensive table of causes of cervical lymph node enlargement

Infections

- Viral upper respiratory tract: an enlarged jugulodigastric (tonsillar) lymph node, is common
- Oral or local bacterial in the drainage area (dental, scalp, ear, nose or throat): including cat-scratch fever and staphylococcal and mycobacterial lymphadenitis
- Systemic:
 - viral (e.g. infectious mononucleosis, cytomegalovirus, HIV infection)
 - bacterial, including syphilis, tuberculosis, brucellosis
 - fungal, including histoplasmosis
 - parasitic; toxoplasmosis, leishmaniasis, tularaemia

Malignant disease

- Oral or in the drainage area (usually oral, scalp, ear, nose or throat; rarely thyroid or gastric)
- Lymphoreticular (leukaemia, lymphoma)
- Langerhans histiocytosis

Others

- Drugs (e.g. phenytoin)
- Mucocutaneous lymph node syndrome (Kawasaki disease)
- Connective tissue disease

► Box 6.2

Most common causes of swellings in the neck at different ages

Child (first decade)

- Lymphadenitis due to viral respiratory tract infection
- Kawasaki disease

Adolescent and teenager

- Lymphadenitis due to viral respiratory tract infection (second decade)
- Bacterial infection
- Glandular fever
- HIV infection
- Toxoplasmosis

Adult (third and fourth decades)

- Lymphadenitis
- Glandular fever syndromes
- HIV infection
- Malignancy

After fourth decade

- Lymphadenitis
- Malignancy

More diffuse swelling of the neck may be caused by:

- infection
- oedema
- haematoma
- malignant infiltration
- surgical emphysema.

The location of a lump or swelling in the neck will often give a good indication of the tissue of origin, and the age of the patient may also help suggest the most likely diagnoses (Box 6.2). The duration of the lesion is also relevant: one that has been present since an early age is likely to be of congenital origin, while a lump appearing in later life and persisting may be malignant.

This chapter concentrates mainly on lymph node disease (Algorithm 6.1).

Enlarged cervical lymph nodes

Lymph nodes can enlarge in a number of disorders (see Box 6.1), often because of disease in the local area of drainage, sometimes because of disease affecting the wider lymphoreticular system (lymph nodes, liver and spleen). It is important, therefore, to consider the whole body when dealing with lymph node swellings; examination of other sites, particularly other nodes, liver and spleen may be necessary.

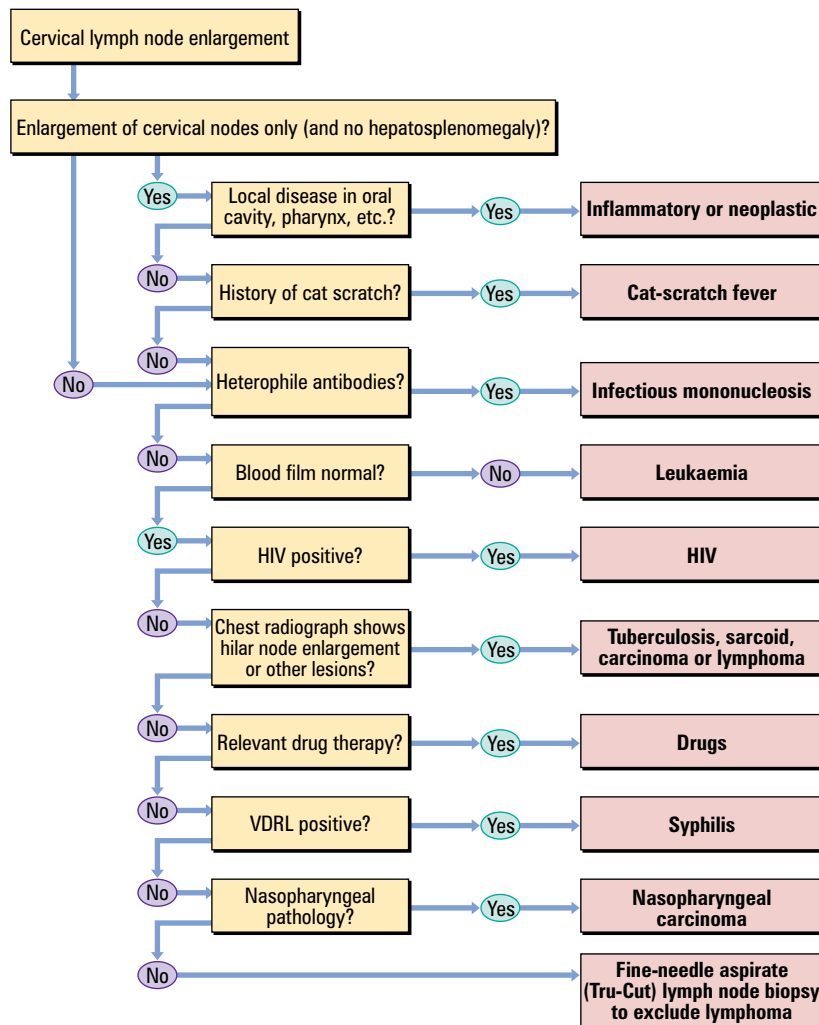
The main complaint with respect to cervical lymph nodes is usually of swelling. The patient may be aware that they have lymphadenopathy, usually termed 'glands in the neck'. Tenderness may have drawn the

patient's attention to their presence. The history should include: date of onset of symptoms; details of any swelling, such as duration and character; and any details of pain experienced, such as duration, character, radiation, aggravating and relieving factors, and associated phenomena. Most disease is detected in nodes in the anterior triangle of the neck, which is bounded superiorly by the mandibular lower border, posteriorly and inferiorly by the sternomastoid muscle, and anteriorly by the mid-line of the neck. Nodes in this site drain most of the head and neck except the occiput and back of the neck. Lymphadenopathy in the anterior triangle of the neck alone is often due to local disease, especially if the nodes are enlarged on only one side.

Enlargement of the cervical lymph nodes alone usually arises because they are involved in an immune response to an infectious agent in the area of drainage and nodes are then often firm, discrete and tender but are mobile (lymphadenitis). The focus of inflammation can usually be found in the drainage area, which is anywhere on the face, scalp and nasal cavity, sinuses, ears, pharynx and oral cavity. Such lymphadenitis only rarely leads to suppuration. The local cause may not always be found despite a careful search; for example, children (especially those of African heritage) occasionally develop a *Staphylococcus aureus* lymphadenitis or a similar problem due to atypical *Mycobacteria* (usually in a sub-mandibular node) in the absence of any obvious portal of infection or any clear explanation for their susceptibility. Enlargement of cervical lymph nodes alone may also occur when there is reactive hyperplasia to a malignant tumour in the drainage area, or metastatic infiltration. The latter may cause the node to feel distinctly hard, and it may become bound down to adjacent tissues ('fixed'), it may not be discrete, and may even, in advanced cases, ulcerate through the skin.

Generalized lymph node enlargement, including cervical nodes may occur in:

- systemic infections, such as the glandular fever syndromes caused by Epstein-Barr virus, cytomegalovirus or toxoplasmosis, and HIV/AIDS. Lymphadenitis in tuberculosis may lead to neck swelling (scrofula) and suppuration (cold abscess)
- inflammatory lesions such as connective tissue diseases; Crohn disease, orofacial granulomatosis and sarcoidosis; and mucocutaneous lymph node syndrome (Kawasaki disease) – these are not known to be infective
- neoplasms of the lymphoreticular system, such as lymphomas, leukaemias and histiocytoses (see Box 6.1), usually cause enlargement of many or all cervical lymph nodes. In some there is clinical involvement of the whole reticuloendothelial system, with generalized lymph node enlargement (detectable clinically in the neck, groin and axilla) and enlargement of both liver and spleen (hepatosplenomegaly). Rosai-Dorfman disease is a rare, non-neoplastic



Algorithm 6.1 Management of cervical lymph node enlargement

histiocytosis most commonly characterized by painless, massive cervical lymphadenopathy.

Infective inflammatory conditions

Viral infections with predominantly upper respiratory and oral manifestations

- Usually several anterior triangle nodes – especially the jugulodigastric nodes – are enlarged, often bilaterally. Posterior triangle nodes are not enlarged and there is, of course, no generalized lymph node enlargement nor hepatosplenomegaly unless there are systemic complications or lesions elsewhere.

- Any viral upper respiratory infection from the common cold to viral tonsillitis can be responsible for enlarged cervical nodes (see Box 6.1).
- Oral viral infections that may cause cervical lymph node swelling are mainly those that also produce mouth ulcers such as:
 - herpes simplex stomatitis
 - herpangina
 - occasionally, herpes zoster of the trigeminal nerve (see Chapter 31).

Viral and other non-bacterial infections with multiple systemic manifestations

In these disorders there are usually several anterior and often posterior triangle nodes enlarged, with generalized enlargement and, in some instances, hepatosplenomegaly. Infections implicated are mainly:

- hand, foot and mouth disease (see Chapter 41)
- viral exanthemata (chickenpox, measles, rubella)
- glandular fever syndromes (Epstein–Barr virus, human herpesvirus 6 and cytomegalovirus infections and toxoplasmosis) and HIV/AIDS.

Acute non-specific bacterial infections

Any bacterial infection in the area of drainage, such as a dental abscess, pericoronitis, sinusitis, or a boil in the nose, can cause enlargement of anterior cervical lymph nodes. Usually only one or two nodes are enlarged, often unilaterally and only in the anterior triangle in most instances. However, lesions on the back of the scalp or neck may cause enlargement of posterior cervical nodes.

Acute specific bacterial infections

Occasionally, specific acute bacterial infections involve lymph nodes, particularly in young children who can develop acute lymphadenitis caused by *Staphylococcus aureus* in the absence of any detectable entry point for the organism. These infections, usually of a submandibular lymph node, should be treated with antibiotics – usually flucloxacillin because the *S. aureus* is often penicillinase-producing. If the lesion is fluctuant and pointing, surgical drainage is needed.

Chronic bacterial infections

- Generalized lymphadenopathy is a typical finding in secondary syphilis (see Chapter 42).
- Tuberculosis and atypical mycobacterial infections (see Chapter 42).
- Brucellosis.
- Cat-scratch disease (see Chapter 42).

Fine-needle aspiration (FNA) of the cervical lymph nodes is the most reliable diagnostic method for tuberculosis (see Chapter 42). Few patients have positive chest radiographs, there is a variable response to the tuberculin skin test, and often a negative culture for mycobacterial organisms.

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a rare genetic immune defect of leucocyte function in which neutrophils and macrophages fail to kill catalase-positive bacteria, such as staphylococci. Patients suffer from recurrent

pyogenic infections and may develop suppurating cervical lymph nodes showing granulomas on biopsy.

Parasitic: toxoplasmosis

For these conditions see Chapter 42.

Mucocutaneous lymph node syndrome

For MLNS (Kawasaki disease) see Chapter 42.

Non-infective inflammatory conditions

- Sarcoidosis (see Chapter 42).
- Crohn's disease (Chapter 42).
- Connective tissue diseases: cervical lymph nodes may be enlarged in rheumatoid arthritis or lupus erythematosus.
- Drug induced (e.g. phenytoin).
- Others (e.g. Kikuchi's disease – a self-limiting illness characterized by pyrexia, neutropenia and cervical lymphadenopathy in young women of Asian descent).

Neoplastic

The neoplasms that usually metastasize to cervical lymph nodes are:

- Oral squamous carcinoma (Fig. 6.2; see Chapter 22).
- Tonsillar cancer – clinically unsuspected tonsillar cancer is the commonest cause of metastasis in a cervical node of unidentified origin. Blind biopsy of the tonsil may reveal a hitherto unsuspected malignancy.
- Nasopharyngeal carcinoma – clinically unsuspected nasopharyngeal cancer is a common cause of metastasis in a cervical node of unidentified origin. Blind biopsy of the nasopharynx, particularly the fossa of Rosenmuller or tonsil, may reveal a hitherto unsuspected malignancy.
- Thyroid tumours.

Usually one or more anterior cervical nodes are involved, often unilaterally in oral neoplasms anteriorly in the mouth, but otherwise not infrequently bilaterally.

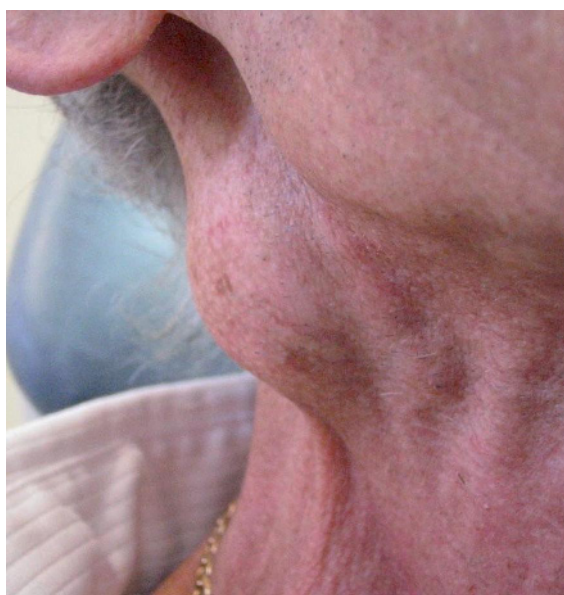


Fig. 6.2 Enlarged jugulodigastric lymph node from metastatic squamous cell carcinoma

Other metastatic neoplasms (other than lymphoid)

Rare causes of cervical metastases include metastases from the stomach or even testicular tumours to the lower cervical nodes, especially the supraclavicular nodes. In occasional patients with a malignant cervical lymph node, the primary tumour is never located.

Lymphoid malignancies

In lymphoid malignancies there is usually swelling both of anterior and posterior cervical lymph nodes together with generalized lymph node enlargement and often hepatosplenomegaly.

Langerhans histiocytosis

Management should be of the underlying condition (see Chapter 42).

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7

Drooling and sialorrhoea

Key points

- Drooling is abnormal if persisting after age 4 years
- Causes include sialorrhoea, swallowing dysfunction, anatomical or neuromuscular anomalies
- Drooling affects patients functionally, socially, psychologically and clinically
- Treatment may be medical or, in extreme cases, surgical.

Introduction

Drooling is defined as saliva beyond the margins of the lips. The condition of increased salivary flow is termed sialorrhoea or pytalism.

Incidence

People at the extremes of age, the chronically debilitated, or those in chronic care facilities, especially associated with cerebrovascular accidents and oesophageal cancer, are especially affected.

Age

Drooling is perfectly normal in healthy infants, but usually stops by about 18 months of age and is considered abnormal if it persists beyond the age of 4 years.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

Drooling is a problem for many children with cerebral palsy, intellectual disability and other neurological conditions, and in adults who have Parkinson's disease or have cerebral palsy, intellectual disability, or have had a stroke, pseudobulbar palsy, or bulbar palsy.

Aetiology and pathogenesis

Drooling is caused either by increased saliva flow (sialorrhoea) that cannot be compensated for by swallowing, or by poor oral and facial muscle control in patients with swallowing dysfunction (secondary sialorrhoea), or by anatomic or neuromuscular anomalies (Table 7.1).

Clinical features

Drooling impacts on patients, families, and caregivers:

- Functionally: saliva soils the clothing of the patient, peers, siblings, parents and caregivers, and furniture, carpets, teaching materials, communicative devices and toys. Clothing and bibs become soiled and need frequent changing.
- Socially: embarrassment may make it difficult for patients to interact with their peers and can lead to isolation.
- Psychologically: stigmatism is common.
- Clinically: unable to manage their oral secretions, affected persons are at increased risk of skin maceration, infection and aspiration. Patients may experience repeated perioral skin breakdown and infections. Aspiration-related respiratory and pulmonary complications are greatest in those with a diminished sensation of salivary flow and hypopharyngeal retention. In rare severe cases, dehydration may become a problem.

Diagnosis

History helps assess the severity and frequency of drooling, and the effect on the quality of life of the patient and family. Quantitative measurements can be helpful for guiding treatment decisions (Table 7.2). Counting the number of bibs or items of clothing soiled each day provides a subjective estimate. Physical findings such as skin maceration on the neck, chest, and hands due to dampness and constant wiping confirm impressions of severity and indicate the need for treatment.

Perform a thorough head and neck examination to include:

- head position and control
- perioral skin condition
- dentition and occlusion: malocclusion, particularly an open bite deformity, is a common finding in patients with cerebral palsy. This can make proper oral hygiene very difficult. Open bite deformities can prohibit closing of the mouth and can mimic nasal obstruction in these patients
- mandible and palatal position
- tongue size and control and the presence of thrusting behaviours

- tonsil and adenoid size
- gag reflex and intraoral tactile sensitivity
- presence of mouth breathing
- nasal obstruction and appearance of tissues upon anterior rhinoscopy
- swallowing efficiency: determined by observation, barium swallow, or fiberoptic endoscopic evaluation of swallowing
- neurologic examination: cranial nerve examination.

Investigations

- Flexible nasopharyngoscopy or lateral neck radiograph to detect adenoid hypertrophy.
- Modified barium swallow to help rule out the contraindications to surgical therapy, including oesophageal motility disorders, oesophageal spasm or aspiration.
- Radiosialography for evaluating salivary secretory function.
- Audiography to detect unilateral hearing impairment in patients considered for tympanic neurectomy or chorda tympani nerve section (because of the risk of hearing loss associated with these procedures).

Table 7.1
Causes of drooling

Excessive saliva production (sialorrhoea)	Decreased swallowing	Anatomic abnormalities	Neuromuscular diseases
Neurologic disorders (especially Riley-Day syndrome, page 344) Otolaryngologic diseases Pregnancy Gastrointestinal causes Liver disease Oral lesions Cholinergic drugs Anticholinesterases	Oropharyngeal infections and obstruction	Macroglossia or tongue thrusting Surgical defects following major head and neck resection	Parkinson's disease, cerebral palsy, intellectual disability, stroke, pseudobulbar palsy, bulbar palsy

Table 7.2
Quantitation of drooling

Condition	Description
Dry	Never drools
Mild	Only lips wet. Occasional drooling – not every day
Moderate frequent drooling	Lips and chin wet – every day
Constant drooling	Severe – clothing soiled Profuse – hands moist and wet

Management

- The impact of drooling on the quality of life is the most important factor in determining the need for treatment.
- The goal is to reduce drooling whilst maintaining a moist, healthy oral cavity.
- Treatment is best done by a team approach, including at least an otolaryngologist, neurologist, surgeon, dentist, orthodontist, speech, occupational and physical therapists.

- Treatment options include medical therapy, radiotherapy and surgery.

Medical therapy

- Oral motor training: exercises can be used to try to normalize muscle tone, increase lip closure, and promote swallowing
- Behaviour therapy; biofeedback and automatic cueing techniques.
- Pharmacotherapeutics attempts to decrease saliva to amounts that can be swallowed (to prevent 'pool

Table 7.3
Medications used to reduce sialorrhoea/drooling*

Agent	How supplied	Adult dosage	Potential adverse effects apart from xerostomia
Glycopyrrolate	Tablets, 1mg or 2mg	Start 0.5mg orally, one to three times daily; titrate to effectiveness and tolerability	Constipation, urinary retention, blurred vision, hyperactivity, irritability
Scopolamine	Patch, 1.5mg	One patch every day	Pruritus at patch site, urinary retention, irritability, blurred vision, dizziness, glaucoma
Botulinum toxin A	Vial, 100 U per vial	Single injections of 10–40 units under ultrasound guidance into all major glands	Pain at injection site

*Adapted from Hockstein et al 2004.

Table 7.4
Surgical treatment of drooling/sialorrhoea*

Surgical therapy	Advantages	Disadvantages
Submandibular gland excision	Good control of sialorrhoea	General anaesthesia needed usually External scar Potential for dental caries
Submandibular duct re-routing	No external scar	General anaesthesia needed usually Potential for anterior dental caries Potential for aspiration Without sublingual gland excision, patient may develop ranula
Parotid duct re-routing	Redirects flow in the stimulated state	General anaesthesia needed usually Risk of sialocele Potential for aspiration
Parotid duct ligation	Simple procedure Decreases flow in the stimulated state	Risk of sialocele
Transtympanic neurectomy	Does not require general anaesthesia Technically simple, fast procedure Useful in elderly patients	Predictable return of salivary function Requires repeating

*Adapted from Hockstein et al 2004.

and drool') without producing xerostomia (Table 7.3), by:

- reducing cholinergic activity, either systemically (e.g. atropine-related oral anticholinergics) or more locally (e.g. sublingual ipratropium spray); because of potential adverse effects, anticholinergic drugs are contraindicated in patients with asthma, or ocular problems, such as glaucoma, or synechia (adhesions) between the iris and lens.
- increasing adrenergic activity (e.g. clonidine patch).
- botulinum toxin type A injected under ultrasound guidance into the parotid and submandibular glands.

Radiotherapy

Irradiation of the major salivary glands has been used to decrease saliva secretion, but has variable success, and the potential risk of late malignancy.

Surgery

Surgery (Table 7.4) is indicated where there is drooling:

- persisting after at least 6 months of conservative therapy

or

- moderate to profuse and in a patient whose cognitive function precludes use of conservative therapy.

Surgical procedures used to control drooling are aimed at decreasing salivary flow, or redirecting the salivary duct flow to a location more advantageous to promote swallowing, and include salivary:

- gland excision
- duct re-routing

- duct ligation or
- nerve sectioning or
- combinations of the above.

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8

Dry mouth (xerostomia)

Key points

Main causes of complaint of dry mouth

- Iatrogenic:
 - drugs
 - irradiation
 - graft-versus-host disease
- Non-iatrogenic disease affecting salivary glands
- Dehydration

Introduction

Saliva is essential to oral health, and patients who have decreased salivary flow (hyposalivation) suffer from lack of oral lubrication, affecting many functions, and may develop infections as a consequence of the reduced defences.

Dry mouth (xerostomia) is a complaint that is the most common salivary problem and is the subjective sense of dryness which may be due to:

- reduced salivary flow (hyposalivation)
- changed salivary composition.

Advancing age is increasingly associated with dry mouth, but this is usually due to medication or disease, rather than age per se. Age does, however, result in an increase in adipose tissue and in a reduction of salivary acini, in salivary secretory reserve and in proteins such as MG1 and MG2 mucins.

Causes

Dry mouth is common in mouth-breathers and during periods of anxiety. Salivation is significantly reduced during sleep. Other than this, the main causes of dry mouth are iatrogenic:

- Drugs are the most common cause (Box 8.1 and Fig. 8.1). There is usually a fairly close temporal relationship between starting the drug treatment or increasing the dose, and experiencing the dry mouth. However, the cause for which the drug is being taken

➤ Box 8.1

More comprehensive list of causes of dry mouth

Iatrogenic causes: drugs

- Atropine, atropinics and hyoscine
- Antidepressants: tricyclic (e.g. amitriptyline, nortriptyline, clomipramine and dosulepin), selective serotonin re-uptake inhibitors (e.g. fluoxetine), lithium and some other antidepressants
- Antihypertensives: may also cause a compositional change in saliva. α_1 antagonists (e.g. terazosin and prazosin) and α_2 agonists (e.g. clonidine) may reduce salivary flow. Beta blockers (e.g. atenolol, propranolol) reduce protein levels
- Phenothiazines
- Antihistamines
- Antireflux agents, such as proton-pump inhibitors (e.g. omeprazole)
- Opioids
- Cytotoxic drugs
- Retinoids
- Bupropion
- Others, such as:
 - Protease inhibitors
 - Didanosine
 - Diuretics
 - Ephedrine
 - Benzodiazepines
 - Interleukin-2

Other iatrogenic causes

- Irradiation
 - External beam
 - Radioiodine
- Graft-versus-host disease

Salivary gland disease

- Salivary aplasia (agenesis)
- Sjögren syndrome
- Sarcoidosis
- Parotidectomy
- Cystic fibrosis
- Ectodermal dysplasia
- Primary biliary cirrhosis
- Infections [HIV, hepatitis C, EBV, human T lymphotropic virus 1 (HTLV-1)]
- Other viruses
- Autonomic cholinergic dysfunction

Dehydration Psychogenic

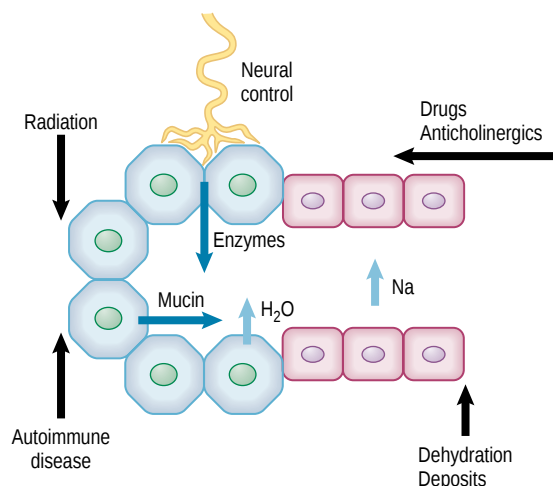


Fig. 8.1 Dry mouth

may also be important. For example, patients with anxiety or depressive conditions may complain of dry mouth even in the absence of drug therapy (or evidence of reduced salivary flow). Drugs with anticholinergic or sympathomimetic or diuretic activity are usually responsible.

- Irradiation if it involves the salivary glands can produce profound xerostomia, such as in treatment for oral cancer, for neoplastic conditions in the head and neck, or in mantle irradiation or total body irradiation (TBI) before haematopoietic stem cell transplant (bone marrow transplant).
- Dehydration, as in diabetes mellitus, diabetes insipidus, hyperparathyroidism or any fever, is an occasional cause of xerostomia.
- Rarely there is cholinergic dysfunction – either congenital or autoimmune.
- Psychogenic causes may underlie the complaint of dry mouth (see page 83).

Clinical features

The patient with hyposalivation may complain of dry mouth alone, or combined with other features, such as dryness of the eyes and other mucosae (nasal, laryngeal, genital), with other eye complaints (inability to cry, blurring, light intolerance, burning, itching or grittiness, and sometimes voice changes). There may also be systemic features (see Sjögren syndrome).

There may be:

- difficulty in swallowing, especially in eating dry foods, such as biscuits (the cracker sign)
- difficulty in controlling dentures in speech and swallowing

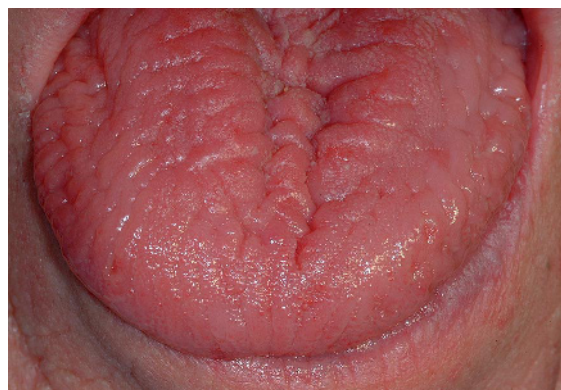


Fig. 8.2 Dryness evident on the tongue



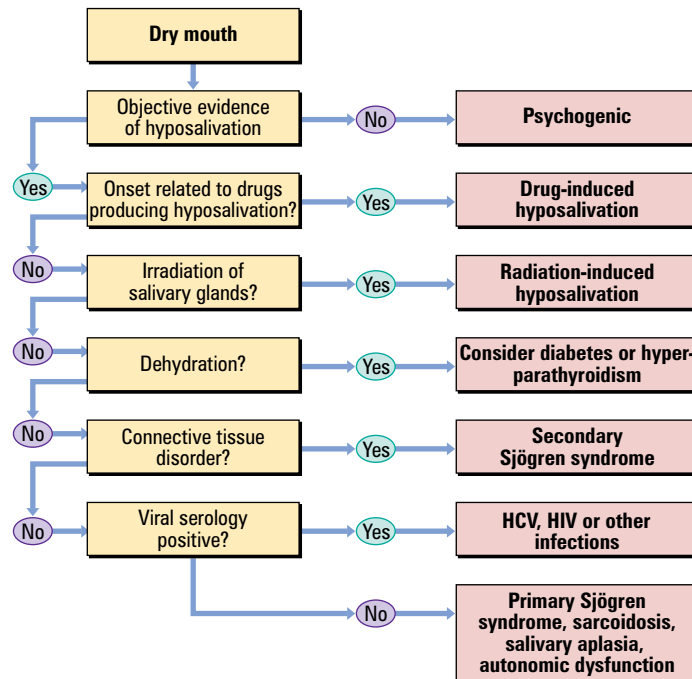
Fig. 8.3 Dryness causing lipstick and food retention

- difficulty in speaking, as the tongue tends to stick to the palate; this can lead to 'clicking' speech
- mouth soreness
- unpleasant taste or loss of sense of taste
- a dry mucosa (**Fig. 8.2**) – the lips adhere one to another and an examining dental mirror may stick to the mucosa
- lipstick or food debris sticking to the teeth (**Fig. 8.3**)
- lack of the usual pooling of saliva in the floor of the mouth
- thin lines of frothy saliva may form along lines of contact of the oral soft tissues or in the vestibule
- saliva not expressible from the parotid duct
- a characteristic lobulated tongue, usually red, with partial or complete depapillation
- complications of xerostomia.

Oral complications

Oral complications of xerostomia may include:

- halitosis (oral malodour)



Algorithm 8.1 Causes of dry mouth (see Ch. 37)

- dental caries, which tends to involve smooth surfaces and areas otherwise not very prone to caries – such as the lower incisor region. Caries can also involve roots and be severe and difficult to control
- candidiasis, which may cause:
 - burning sensation
 - taste changes
 - intolerance of acids and spices
 - mucosal erythema
 - lingual filiform papillae atrophy
 - angular stomatitis (angular cheilitis)
- ascending (suppurative) sialadenitis, which presents with pain and swelling of a major salivary gland, and sometimes purulent discharge from the duct.

Diagnosis

Hyposalivation is a clinical diagnosis, made predominantly on the basis of the history and examination. The aims are to document the degree of salivary dysfunction and to determine the cause (Algorithm 8.1).

Salivary function studies

It can be helpful to document salivary function not just from the history and examination findings, but also by salivary function studies, which include studies of the

salivary flow rates (sialometry), sialography, salivary scintiscanning and ultrasonography.

Salivary flow rates (sialometry)

Salivary flow rate estimation (Fig. 8.4) is simple, inexpensive and sensitive but a non-specific indicator of salivary gland dysfunction usually carried out by one of two possible methods:

- unstimulated whole saliva flow rate (this more closely correlates with symptoms of xerostomia than do stimulated flow rates). The test should be standardized by being carried out first thing in morning after overnight fasting; no food or drink for at least 1 hour before the test; no smoking for at least 1 hour before the test. Allow the patient to dribble into a measuring container over 15 minutes. A resting secretion rate of <1.5ml in 15 minutes is decreased: in a normal person the unstimulated whole saliva flow rate exceeds 1.5ml/15 minutes (0.1ml/minute).
- stimulated saliva flow rate. Use various means of stimulation, such as 10% citric acid dropped onto the tongue, and collect parotid saliva using a Carlsson-Crittenden cup placed over Stensen's papilla. A flow of <0.5ml per gland in 5 minutes or <1ml per gland in 10 minutes is decreased. In normal persons the flow should well exceed 1ml/minute.



Fig. 8.4 Dryness evident on sialometry

Sialography

Sialography, in which radio-opaque dye, often iodine-based, is introduced into the salivary duct, is non-specific. It may be of value if there is dilatation or duct obstruction (e.g. by a calculus, though this rarely causes dryness), but carries risks of discomfort and infection.

Salivary scintiscanning

Salivary scintiscanning non-invasively examines all major salivary glands simultaneously, but is associated with a small radiation hazard since technetium-99m, a γ -emitting radionuclide is used. It is not always available and is expensive.

Determination of the cause of xerostomia

The history and examination may help to determine the cause of dry mouth, but investigations may be indicated to exclude systemic diseases noted above. Commonly indicated investigations may thus include the following:

- Eye tests, using Schirmer test of lacrimal flow (Fig. 8.5), and slit-lamp examination, mainly to exclude Sjögren syndrome (see Ch. 36).
- Urinalysis, mainly to exclude diabetes.
- Blood tests:
 - erythrocyte sedimentation rate (ESR) or plasma viscosity – a non-specific test mainly to exclude Sjögren syndrome or sarcoidosis
 - antinuclear antibodies (ANA) – including SS-A and SS-B antibodies, mainly to exclude Sjögren syndrome and sarcoidosis (see Ch. 36)



Fig. 8.5 Tests for lacrimation

- rheumatoid factor (RF), mainly to exclude Sjögren syndrome
- serum immunoglobulin levels, a non-specific test mainly to exclude connective tissue diseases
- serum angiotensin-converting enzyme (SACE), mainly to exclude sarcoidosis
- serum calcium and phosphate, mainly to exclude hyperparathyroidism
- serology, to exclude viral causes
- blood glucose, to exclude diabetes.
- Imaging:
 - chest radiography, mainly to exclude sarcoidosis
 - ultrasonography, mainly to exclude Sjögren syndrome or neoplasia
 - magnetic resonance imaging (MRI), mainly to exclude Sjögren syndrome.
- Salivary biopsy may be indicated if there is suspicion of organic disease of the salivary glands. Although it is perfectly possible to biopsy the parotid or other major gland, there is a small risk of nerve damage or salivary fistula, and an extraoral approach will leave a small scar. Therefore, biopsy of minor salivary glands is usually done. Glands in the lower labial mucosa are selected (labial salivary gland biopsy), since they are readily biopsied through a simple incision in the labial mucosa under local analgesia. The incision is paramedian, placed in the lower labial mucosa (avoiding any clinically obvious mucosal lesions, which could confuse the diagnosis) and is thus not visible externally. Four to six lobules of salivary glands should be removed. The wound is closed with one or two sutures and, apart from mild discomfort in many and anaesthesia or hypoaesthesia in some cases, complications are rare.

It is important to recognize that some patients complaining of a dry mouth have no evidence of a reduced salivary flow or a salivary disorder. There may then be a psychogenic reason for the complaint.

Patient information sheet

DRY MOUTH

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Saliva usually helps swallowing, talking and taste, and protects the mouth and teeth.
- Where saliva is reduced there is a risk of dental decay (caries), halitosis, altered taste sensation, mouth soreness and infections.
- Saliva may be reduced after radiotherapy or chemotherapy or the use of various drugs, after bone marrow transplants, in diabetes, in some viral infections, in anxiety/stress/depression, or in some salivary gland disorders.

Diagnosis

This is a clinical diagnosis mainly, but investigations may be indicated, including:

- blood tests
- eye tests
- urine analysis
- salivary flow rate tests
- salivary gland biopsy.

A simple biopsy, under local anaesthesia, of small glands inside the lower lip is quick and has few adverse effects except occasional minor anaesthesia.

- X-rays or scans.
- Chest X-ray.
- Sialography – your saliva is dyed and the amount measured.
- Scintiscanning – your saliva is radioactively marked and the amount measured.
- Ultrasound, like an X-ray but for the soft tissues.

10 steps to manage dry mouth

- Sip on juices and other fluids throughout the day. Dryness can be combated by rinsing with water. Take small sips of fluids with each bite of food at meal times. Keep water at your bedside.
- Replace missing saliva with salivary substitutes (Artificial Saliva, Glandosane, Luborant, Oralbalance, Saliva Orthana, Salivace, Saliveze).
- Stimulate saliva with:
 - sugar-free chewing gums (EnDeKay or Orbit)
 - diabetic sweets
 - Salivix, if advised
 - drugs that stimulate salivation (Salagen) if advised by the specialist.
- Avoid spicy or dry foods or hard crunchy foods such as biscuits even when dunked in liquids. Take small bites and eat slowly. Eat soft, creamy foods (casseroles, soups), or cool foods with a high liquid content (melon,

Patient information sheet—cont'd

grapes, ice cream). Moisten foods with gravies, sauces, extra oil, margarine, salad dressings, sour cream, mayonnaise or yogurt. Pineapple has an enzyme that helps clean the mouth.

- Always take water or non-alcoholic drinks with meals.
- Avoid anything that may worsen dryness, such as:
 - drugs (e.g. antidepressants, unless they are necessary)
 - alcohol (including in mouthwashes)
 - smoking
 - caffeine (coffee, some soft drinks)
 - mouth-breathing.
- Protect against dental caries by avoiding sugary foods/drinks and by:
 - reducing sugar intake (avoid snacking and eating last thing at night)
 - avoiding sticky foods such as toffee
 - keeping your mouth very clean (twice daily toothbrushing and flossing)
 - using a fluoride toothpaste
 - using fluoride gels or mouthwashes daily before going to bed
 - having regular dental checks.
- Protect against thrush and halitosis by:
 - keeping your mouth very clean
 - keeping your mouth as moist as possible
 - rinsing twice daily with chlorhexidine (Chlorohex, Corsodyl, Eludril)
 - leaving dentures out at night
 - disinfecting dentures in hypochlorite (e.g. Milton, Dental)
 - using antifungals if recommended by a specialist.
- Protect the lips with a lip salve.
- Consider a humidifier for the bedroom.

Management

- Any underlying cause of xerostomia should, if possible, be rectified; for example, xerostomia-producing drugs may be changed for an alternative, and causes such as diabetes should be treated.
- Efforts should be made to avoid factors that may increase dryness, such as:
 - dry hot environments
 - dry foods such as biscuits
 - drugs (e.g. tricyclic antidepressants or diuretics)
 - alcohol (including alcohol-based mouthwashes)
 - smoking
 - beverages that produce diuresis (coffee and tea).
- The mouth should be hydrated as regularly as possible. The lips may become dry, atrophic and susceptible to cracking and thus should be kept moist using a water-based lubricant or a lanolin-based product rather than one containing petroleum-derived lubricants (e.g. Vaseline). Olive oil, vitamin E or lip balm may help.



Fig. 8.6 Salivary substitute



Fig. 8.8 Salivary substitute



Fig. 8.7 Salivary substitute

- Salivary substitutes may help symptomatically. Various are available, including:
 - Water or ice chips: frequent sips of water are generally more effective than synthetic salivary substitutes.
 - Synthetic salivary substitutes (Figs 8.6–8.8), which vary in properties such as patient acceptability, fluoride content and pH (Table 8.1). Synthetic salivary substitutes usually contain: carboxymethylcellulose (UK: Glandosane, Luborant (contains fluoride), Salivace, Saliveze. USA: Moi-Stir, Orex, Salivart, Xero-Lube, Mouth-Kote), mucin (Saliva Orthana; also contains xylitol and fluoride) or glycerate polymer (Oral Balance; also contains xylitol, glucose oxidase and lactoperoxidase). A home preparation can be made using $\frac{1}{4}$ teaspoon of glycerine in 8 ounces of water.

- Salivation may be promoted by using a stimulant:
 - chewing gums (containing sorbitol or xylitol, not sucrose) (Fig. 8.9)
 - diabetic sweets
 - cholinergic drugs that stimulate salivation (sialogogues), such as pilocarpine, bethanecol, cevimeline or anetholetrithione.
- Oral complications, such as dental caries, should be prevented and treated:
 - Dietary control of sucrose intake is important.
 - Regular dental checks are required and monitoring of *Streptococcus mutans* counts may be helpful.
 - Topical fluorides reduce caries risk by reducing demineralization and by increasing remineralization.
 - Full-strength fluoride toothpastes containing 1000–1500 ppm fluoride should be used at least twice daily. Higher content pastes may be indicated.
 - Fluoride rinses of 0.05% sodium fluoride should be used before retiring to bed at night.
 - Fluoride gel products provided in tightly adapted vacuform mouth guard carriers are also useful. Fluorides may be usefully applied in the dental office, and daily at home (sodium fluoride gels or 0.4% stannous fluoride gels).
 - Glass ionomer restorations can be useful since they release fluoride.
 - It is best to wait until a year of no new caries has elapsed before constructing new crowns.
- Oral complications such as candidiasis should be treated:
 - A rinse or swab from the oral mucosa should be taken to confirm the presence of candidiasis if there is soreness and signs of inflammation. A commercial kit such as Ori-cult may be helpful.

Table 8.1
Some sialogogues and salivary replacements

Agent	Use	Comments
<i>Sialogogues</i>		
Pilocarpine (Salagen), or cevimeline	5mg up to 3 times daily with food	Patient may be unable to see well enough to drive or operate machinery Contraindicated in asthma, chronic obstructive airways disease, glaucoma and pregnancy Care with cardiac disease
Salivix	Malic acid	Pastille
<i>Salivary replacements (artificial salivas)</i>		
Glandosane	Sodium carboxymethylcellulose base	Spray
Luborant	Sodium carboxymethylcellulose base	Spray
Oralbalance	Lactoperoxidase, glucose oxidase and xylitol	Gel
Saliva Orthana	Mucin	Spray containing fluoride, or lozenge May be unsuitable if there are religious objections to porcine mucin
Salivace	Sodium carboxymethylcellulose base	Spray
Saliveze	Sodium carboxymethylcellulose base	Spray

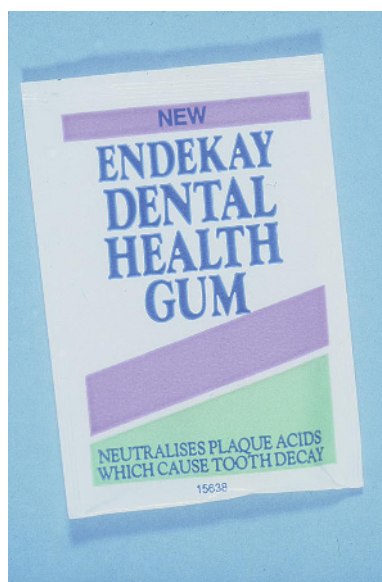


Fig. 8.9 A chewing gum

- Dentures should be left out of the mouth at night and stored in sodium hypochlorite solution, benzalkonium chloride or chlorhexidine.
- Chlorhexidine, used in aqueous solution as a mouth rinse, has both antibacterial and antifungal effects, and there may be advantages to its use in dentate patients, due to some effect of chlorhexidine against cariogenic bacteria as well as *Candida*.
- Antifungals should be used, until there is no evidence of mucosal erythema and symptoms, and should be continued for at least 2 weeks more, to reduce the risk of recurrence. Topical antifungals tend to be most effective, since salivation is low and thus salivary antifungal delivery is not good. Topical antifungals are available as tablets which can be allowed to dissolve intraorally, resulting in contact with mucosa while dissolving in the mouth. Unfortunately, the oral tablets typically are sugar-sweetened, yet it is important to avoid sucrose-sweetened products where natural teeth are present. It has become common practice to use the vaginal antifungal tablets intraorally as these are not sucrose-sweetened. However, if the mouth is extremely dry, tablets may not dissolve, and in these cases liquid products are best. The polyenes, nystatin and amphotericin, which bind to membrane sterols in fungal cell membranes, damaging cell membranes and leading to death of the microorganisms, are effective topically. Fluconazole systemically is also effective against oropharyngeal candidiasis. An antifungal, such as miconazole gel or amphotericin or nystatin ointment, should be spread on dentures or appliances before re-insertion.
- Oral complications such as bacterial sialadenitis should be treated:
 - A swab should be collected of any pus expressed from the salivary duct, for bacterial culture and antibiotic sensitivities.
 - Acute sialadenitis needs treating, usually with a penicillinase-resistant antibiotic, such as flucloxacillin.

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9

Halitosis (oral malodour)

Key points

Main causes of halitosis

- Oral biofilm or sepsis
- Dry mouth
- Starvation
- Smoking
- Some foods
- Drugs
- Systemic disease:
 - diabetes
 - respiratory and nasal
 - gastrointestinal
 - hepatic
 - renal
 - psychogenic

- periodontitis
- pericoronitis and other types of oral sepsis
- infected extraction sockets
- residual blood postoperatively
- debris under bridges or appliances
- ulcers
- dry mouth.

The organisms implicated include:

- *Porphyromonas gingivalis*
- *Prevotella intermedia*
- *Fusobacterium nucleatum*
- *Bacteroides forsythus*
- *Treponema denticola*.

These anaerobes produce the chemicals that cause malodour in many instances, which include:

- volatile sulphur compounds (VSCs) (mainly methyl mercaptan, hydrogen sulphide and dimethyl sulphide)
- polyamines (putrescine and cadaverine)
- short-chain fatty acids (butyric, valeric and propionic acids).

Introduction

Halitosis, from the Latin for breath *halitus*, is a fairly common complaint found mainly in adults. Halitosis is a problem analogous to body odour and is the cause for serious concern by many sufferers. Up to 30% of adults over 60 years old report either being conscious of their oral malodour, or having been told by others they have it. However, not all persons who believe they have halitosis actually have any malodour; this can be a real clinical dilemma, and appears to have a psychogenic basis.

Oral malodour is common on awakening (*morning breath*) and is then usually a consequence of low salivary flow and oral cleansing during sleep. This rarely has any special significance, and can be readily rectified by eating, oral cleansing and rinsing the mouth with fresh water.

Malodour at other times is often the consequence of eating various foods such as garlic, onion or spices, or of habits such as smoking or drinking alcohol. The avoidance of these foods and habits is the best prevention.

Halitosis that is not due to these causes is most often a consequence of oral bacterial activity (Fig. 9.1), typically from anaerobes arising from:

- poor oral hygiene (Figs 9.2 and 9.3)
- gingivitis (especially necrotizing gingivitis)

The tongue is often the location of many of the organisms implicated. Prevention of infective processes, improvement of oral hygiene, and sometimes the use of antimicrobial therapy can usually manage this type of halitosis.

Halitosis in a very few cases originates distal to the tonsils (Box 9.1). Such causes that may be responsible for oral malodour include the following:

- Starvation, probably partly due to oral stagnation
- Drugs:
 - amphetamines
 - chloral hydrate
 - cytotoxic agents
 - dimethyl sulphoxide (DMSO)
 - disulfiram
 - nitrates and nitrites
 - phenothiazines
 - solvent abuse
- Diabetic ketosis: the breath may smell of acetone
- Respiratory disease. Nasal sepsis or foreign bodies, or infection of the paranasal sinuses or respiratory tract

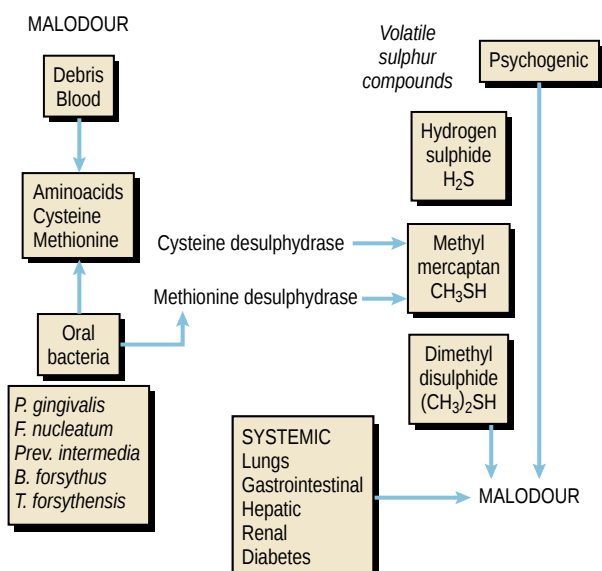


Fig. 9.1 Causes of malodour



Fig. 9.2 Materia alba and marginal gingivitis



Fig. 9.3 Plaque accumulation and gingivitis.

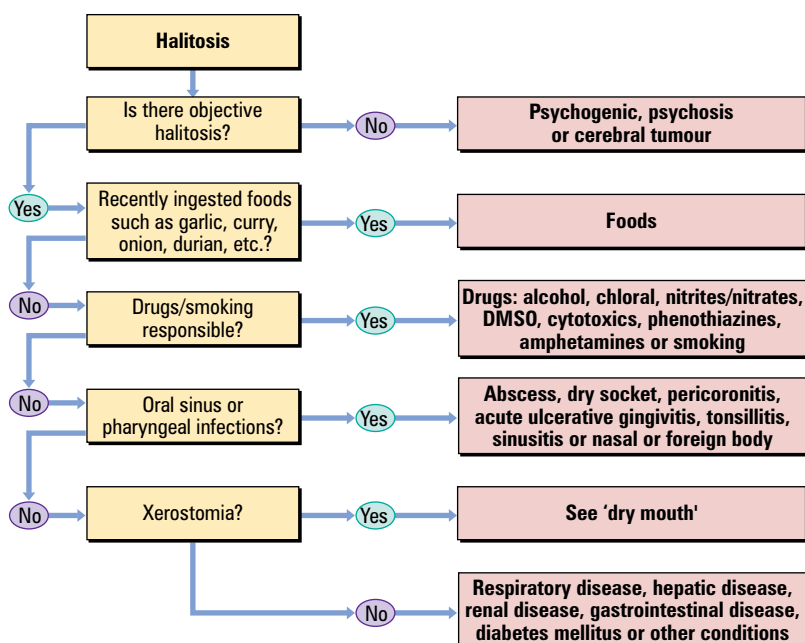
may be a cause. In children, the insertion of foreign bodies, such as small toys into the nose, and subsequent sepsis, is a common cause of halitosis. At any age infections in the respiratory tract, such as tonsillitis, bronchitis, bronchiectasis or other lung infections, or tumours, may be responsible

- Gastrointestinal disease. Although *Helicobacter pylori* has been suspected as a cause, it is an uncommon aetiology
- Hepatic failure
- Renal failure
- Psychogenic or psychosomatic factors. In some patients, no evidence of halitosis can be detected even with objective testing, and the halitosis may be attributed to a form of delusion or monosymptomatic hypochondriasis (self-halitosis, halitophobia). Such patients rarely wish to visit a psychological specialist because they fail to recognize their own psychological condition and never doubt they

Box 9.1

Causes of halitosis

- Oral sepsis
- Dry mouth
- Starvation
- Smoking
- Some foods
- Drugs
- Systemic disease:
 - diabetic ketosis
 - respiratory and nasal disease
 - gastrointestinal disease
 - hepatic failure
 - renal failure
- Psychogenic factors



Algorithm 9.1 Halitosis (DMSO, dimethyl sulphoxide)

have oral malodour. Other people's behaviour, or perceived behaviour, such as apparently covering the nose or averting the face, is typically misinterpreted by these patients as an indication that their breath is indeed offensive. Such patients may have latent psychosomatic illness tendencies and may be mentally immature. Anxiety may also increase malodour.

Many of these patients will adopt behaviour to minimize their perceived problem, such as covering the mouth when talking, avoiding or keeping a distance from other people, using chewing gum, mints, mouthwashes or sprays designed to reduce malodour, or excessively cleaning their tongue or mouth.

Diagnosis

Diagnosis (Algorithm 9.1) is mainly clinical, made from:

- full history
- examination
- assessment of halitosis, usually by simply smelling the exhaled air (organoleptic method) first from the mouth (with nose closed by pinching nostrils) then from the nose (with patient's mouth closed).

Some centres are able to also undertake objective measurements of the agents responsible:

- Volatile sulphur compounds, such as hydrogen sulphide and methyl mercaptan, using a halimeter



Fig. 9.4 Hand held halimeter

(Interscan Corp., Chatsworth, CA, USA) (Figs 9.4 and 9.5). Other compounds, however, are not detected.

- Oral flora, such as by the BANA (benzoyl-arginine-naphthyl-amide) test or dark field microscopy, which can be helpful, at least for patient education.



Fig. 9.5 Halimeter

Patient information sheet

ORAL MALODOUR (HALITOSIS)

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

Halitosis

- Is common on awakening.
- Is often far more obvious to the sufferer than others.
- If real is usually caused by diet, habits, dental plaque or oral disease.
- Can be measured with a halimeter.
- Often improves with oral hygiene.
- Can sometimes be caused by conditions of the sinuses, nose or throat.
- Is rarely caused by more serious disease.

10 steps to control breath odour

- Treat any identifiable cause (this may need antimicrobials).
- Avoid odiferous foods such as onions, garlic and spices.
- Avoid habits that may worsen breath odour, such as:
 - alcohol
 - smoking.
- Take regular meals.
- Eat fresh fruit regularly: pineapple has an enzyme that helps clean the mouth.
- Brush your teeth after eating.
- Keep oral hygiene regular and good by:
 - prophylaxis
 - toothbrushing
 - flossing
 - rinsing twice daily with chlorhexidine (Chlorohex, Corsodyl, Eludril) cetylpyridinium, Listerine or other mouthwashes.
- Brush your tongue before going to bed: use a tongue scraper if that helps.
- Keep your mouth as moist as possible by using:
 - sugar-free chewing gums
 - diabetic sweets.
- Use proprietary 'fresh breath' preparations.
- If you have dentures, leave them out at night and in hypochlorite or chlorhexidine.

Management

The management of halitosis includes the following:

- Patient education.
- Treating the cause. Medical help may be required to manage patients with a systemic background to their complaint.
- Avoiding smoking, foods such as onions, garlic and durian, and vegetables such as cabbage, cauliflower and radish.
- Regular meals and good oral hygiene, the latter involving dental prophylaxis, toothbrushing, flossing and tongue cleaning (with a scraper; this is best done before going to bed since scraping early during the day may induce retching).
- Oral antiseptics. Generally, it is recommended that mouthwashes should be used two or three times daily for at least 30 seconds. These include products containing chlorhexidine (which is effective but may cause tooth-staining and occasional other adverse effects), cetylpyridinium, triclosan, essential oils or zinc chloride. All appear from published reports to be effective at reducing malodour, and most will reduce malodour for at least 3 hours, but some can be effective for much longer periods. Such products include a mouthwash which has two phases consisting of natural essential oils, triclosan and a water solution of cetylpyridinium chloride, plus sodium fluoride, and a toothpaste containing triclosan and a copolymer. In addition, chewing gum, parsley, mint, cloves or fennel seeds and the use of proprietary 'fresh breath' preparations may help.

Other products are available, such as those containing chlorine dioxide, and α -ionone, but the presented evidence for their efficacy is currently weak. A multitude of these products is available over the counter, testimony to the extent of the perceived or, indeed real, problem of halitosis.

- In recalcitrant cases, the specialist empirically may use a 1-week course of metronidazole 200mg three times daily in an effort to eliminate unidentified anaerobic infections.
- A number of 'fresh breath' clinics have been established, and may assist patients with the problem of halitosis.

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10 Lumps and swellings

Key points

Causes of oral lumps and swellings

- Normal anatomy
- Lesions:
 - developmental
 - inflammatory
 - traumatic
 - hormonal
 - drug-induced
 - neoplasms
 - fibro-osseous lesions
 - others

Introduction

Swelling and lumps in the mouth are common, and the tongue often detects even very small swellings or patients may notice a lump because it is sore. Some individuals discover and worry about normal anatomical features, such as the parotid papilla, foliate papillae on the tongue, or the pterygoid hamulus. Most patients have only a passing interest in their mouths, but some examine their mouths out of idle curiosity, and some through fear (perhaps after hearing of someone with 'mouth cancer'). In contrast, many oral cancers are diagnosed far too late, often after being present several months, because the patient ignores the swelling. Some 'lumps' become ulcers, as in various bullous lesions and in malignant neoplasms. Many different conditions may present as oral lumps or swellings, causes including the following:

- The mouth's normal anatomy, such as tongue papillae (Figs 10.1 and 10.2).
- Developmental: unerupted teeth, and tori are common causes of swellings related to the jaws. Cysts and hamartomas may present as a swelling.
- Inflammatory; dental abscess is one of the most common causes of oral swelling. Non-infective inflammatory causes include Crohn's disease, orofacial granulomatosis and sarcoidosis.
- Traumatic: haematoma may cause a swelling at the site. The flange of a denture impinging on the vestibular



Fig. 10.1 Foliate papillae



Fig. 10.2 Circumvallate papillae

mucosa may stimulate a reactive irregular hyperplasia – the so-called denture granuloma or denture-induced hyperplasia. Pyogenic granuloma may cause a lump.

- Hormonal: pregnancy may result in generalized gingival swelling (pregnancy gingivitis) or a discrete lump (pregnancy epulis – really a pyogenic granuloma). Diabetes predisposes to periodontal abscesses and occasionally giant cell lesions are seen in hyperparathyroidism.
- Drug induced: a range of drugs can produce gingival swelling – most common are phenytoin, ciclosporin and calcium channel blockers.
- Neoplasms, such as carcinoma (Fig. 10.3), lymphoma, Kaposi sarcoma, salivary gland tumours and others, are important causes of oral swellings (Fig. 10.4). Occasionally metastatic malignant disease or leukaemia may present as a lump.



Fig. 10.3 Carcinoma causing gingival swelling



Fig. 10.4 Salivary neoplasm causing palatal swelling



Fig. 10.5 Papilloma causing palatal swelling

- Viral lesions: papillomas (Fig. 10.5), common warts (verruca vulgaris), genital warts (condyloma acuminatum) and focal epithelial hyperplasia (Heck's disease) are all caused by papilloma viruses.

- Fibro-osseous lesions: fibrous dysplasia and Paget's disease can result in hard jaw swellings.
- Deposits: amyloid disease and other deposits can cause swellings.

Diagnosis

- Position: the anatomical position should be defined as accurately as possible. The proximity of the lump to other structures (e.g. teeth, dentures) should be noted. Does the swelling have an orifice, or sinus? If fluid is draining from the opening, is it clear, cloudy or purulent? Other similar or relevant changes elsewhere in the oral cavity should be noted (Box 10.1).
- Midline lesions tend to be developmental in origin (e.g. torus palatinus; see Ch. 39).
- Determine whether the lump is bilateral, since most neoplastic lumps are unilateral.
- Number of swellings, particularly with regard to whether the lesion is bilaterally symmetrical and thus possibly anatomical. Multiple lesions suggest an infective or occasionally developmental origin.
- Size: the size should always be measured and recorded. A diagram may be helpful. Thus, significant changes that may occur later can be recognized. In contrast, vague comments describing the swelling as 'medium' or 'large' are unhelpful.
- Shape: many swellings have characteristic shapes that point towards the diagnosis. Thus swelling of the parotid gland often fills in the space between the posterior border of the mandible and the mastoid process.
- Colour and temperature: brown or black pigmentation may be due to a variety of causes, such as melanoma. Purple or red may be due to an angioma (Fig. 10.6) or Kaposi sarcoma. Is the lump pale in colour (suggesting underlying fibrosis, or soft tissues stretched over bony enlargement); red (suggesting inflammation); or deep red (suggesting haemangioma or giant-cell epulis)? Any variations in colour within the lump (e.g. a 'pointing' abscess) should be observed. The skin and mucosa overlying acute inflammatory lesions, such as an abscess, is frequently red and warm.
- Tenderness: inflammatory swellings, such as an abscess, are characteristically tender, although clearly palpation must be gentle to avoid excessive discomfort to the patient.
- Discharge: note any discharge from the lesion (clear fluid, pus, blood).
- Movement: the mobility of any swelling should be tested to determine if it is fixed to adjacent structures or the overlying skin/mucosa, such as often happens with a neoplasm.

► Box 10.1

Lumps in the mouth by main location

Gingiva

- Abscesses
- Amyloidosis
- Chronic gingivitis
- Chronic granuloma (Crohn's disease, orofacial granulomatosis, sarcoidosis)
- Cysts
- Drugs:
 - phenytoin
 - ciclosporin
 - calcium channel blockers
- Exostoses
- Fibrous epulis
- Giant cell tumour
- Hereditary gingival fibromatosis
- Hyperplastic gingivitis
- Hypoplasminogenaemia
- Neoplasm (carcinoma, leukaemia, lymphoma, Kaposi's sarcoma, midline lethal granuloma, Wegener's granulomatosis)
- Pregnancy
- Pyogenic granuloma
- Scurvy

Buccal

- Angioma
- Chronic granuloma (Crohn's disease, orofacial granulomatosis, sarcoidosis)
- Fibrous lump
- Mucocele
- Neoplasm (carcinoma, lymphoma, salivary gland neoplasm, Kaposi's sarcoma)

Palate

- Dental abscess
- Neoplasm (carcinoma, lymphoma, salivary gland neoplasm, Kaposi's sarcoma)
- Papilloma
- Torus palatinus
- Unerupted teeth
- Others

Tongue

- Amyloidosis
- Angioma or lymphangioma
- Fibrous lump
- Granular cell tumour
- Haematoma
- Neoplasm (carcinoma, lymphoma, Kaposi's sarcoma, salivary tumour)
- Papillitis
- Others

- Consistency: this may vary from soft and fluctuant to hard. Fluctuation refers to the presence of fluid within a swelling, such as a cyst. This sign is elicited by detecting movement of fluid when the swelling is compressed.



Fig. 10.6 Haemangioma

Palpation may then help assessment of its contents and these can be put into such categories as fluid (fluctuant because of cyst fluid, mucus, pus or blood), soft, firm, or hard like a carcinoma (indurated). Palpation may cause the release of fluid (e.g. pus from an abscess) or cause the lesion to blanch (vascular) or occasionally cause a blister to appear or expand (Nikolsky sign). Sometimes palpation causes the patient pain (suggesting an inflammatory lesion). The swelling overlying a bony cyst may crackle (like an egg-shell) when palpated. Palpation may disclose an underlying structure (e.g. the crown of a tooth under an eruption cyst) or show that the actual swelling is in deeper structures (e.g. submandibular calculus). Bimanual palpation should be used when investigating lesions in the floor of the mouth, cheek, and occasionally the tongue.

- Surface texture: the surface of a swelling may vary from the uniform smooth texture of many fibrous lumps to the grossly irregular. The surface characteristics should be noted: papillomas have an obvious anemone-like appearance; carcinomas and other malignant lesions tend to have a pebbly surface and may ulcerate. Abnormal blood vessels suggest a neoplasm.
- Ulceration: some swellings may develop superficial ulceration, such as squamous cell carcinoma. The character of the edge of the ulcer and the appearance of the ulcer base should also be recorded. Ulcers should be examined for induration, which is indicative of malignancy.
- Margin: the margins of the swelling may be well-defined or poorly defined. This may give some indication of the underlying pathology. Thus, ill-defined margins are frequently associated with malignancy, whereas clearly defined margins are suggestive of benign growth.
- Associated swelling: some conditions are associated with multiple swellings of a similar nature inside or outside the mouth (e.g. neurofibromatosis).

► Box 10.2

More comprehensive table of conditions that may present as oral lumps or swellings

Normal

- Pterygoid hamulus
- Parotid papillae
- Foliate papillae
- Unerupted teeth

Developmental

- Haemangioma
- Lymphangioma
- Maxillary and mandibular tori
- Hereditary gingival fibromatosis
- von Recklinghausen's neurofibromatosis

Cystic

- Eruption cysts
- Developmental cysts
- Cysts of infective origin

Inflammatory

- Abscess
- Pyogenic granuloma
- Crohn's disease
- Orofacial granulomatosis
- Sarcoidosis
- Wegener's granulomatosis
- Infections
- Insect bites
- Others

Traumatic

- Haematoma
- Epulis
- Epithelial polyp
- Denture granulomas

Hormonal

- Pregnancy epulis/gingivitis
- Oral contraceptive (pill gingivitis)
- Brown tumour of hyperparathyroidism

Drugs

- Phenytoin
- Ciclosporin
- Calcium channel blockers

Neoplasms

- Benign (and warts)
- Malignant

Fibro-osseous lesions

- Fibrous dysplasia
- Paget's disease

Deposits

- Amyloidosis
- Hypoplasminogenaemia (fibrin deposits)
- Other deposits

Others

- Angioedema

The nature of many lumps cannot be established without further investigation:

- Any teeth adjacent to a lump involving the jaw should be tested for vitality, and any caries or suspect restorations investigated.
- The periodontal status of any involved teeth should also be determined.
- Imaging is required whenever lumps involve the jaws, and should show the full extent of the lesion and possibly other areas. Special radiographs (e.g. of the skull, sinuses, salivary gland function), computed tomography (CT scans), magnetic resonance imaging (MRI) or ultrasonography may, on occasions, be indicated. Photographs may be useful for future comparison.
- The medical history should be fully reviewed as systemic disorders may be associated with intra-oral or facial swellings (Box 10.2). Blood tests may be needed, particularly if there is suspicion that a blood dyscrasia or endocrinopathy may underlie the development of the lump.

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11 Pain

Key points

Causes of orofacial pain

- Local disease, especially odontogenic
- Neurological
- Vascular
- Functional (psychogenic)
- Referred pain

Pain in the head, face, mouth, or teeth is the main reason why many patients consult their dental professional.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is not only a sensory experience, its relation with tissue damage may not be constant and it is often associated with affective and cognitive responses.

Pain is a complicated process that involves an intricate interplay between a number of important chemicals found naturally in the nervous system. The neural mechanisms by which pain is perceived are part of a process that involves four major steps:

- transduction
- transmission
- perception
- modulation.

The transduction and transmission steps relate to the neurochemical signals of actual or impending tissue damage (nociceptive stimuli). Nociception is the physiological process of activation of specialized neural pathways, specifically by tissue damaging or potentially damaging stimuli:

- Injury:
 - activates nociceptors, releasing peptides (tachykinins) – substance P and neurokinin A – which play a role in pain responses
 - releases substance P, which acts on mast cells to release histamine and on vessels to release bradykinin

- releases algogenic substances or tissue autocoids, bradykinin and prostaglandins from damaged cells, platelets or mast cells.
- Prostaglandins stimulate nerves at the site of injury and can cause inflammation and fever.
- Cytokines can trigger pain by promoting inflammation.
- Nerve damage may:
 - upregulate galanin and vasoactive intestinal polypeptide (VIP) in dorsal ganglion cells
 - downregulate substance P, somatostatin and calcitonin gene-related peptide (CGRP).
- Many of the small peptides found in the nervous tissue function as synaptic neurotransmitters:
 - excitatory neuropeptides: Substance P, neurokinin A
 - inhibitory neuropeptides: somatostatin, enkephalins
 - others: CGRP, VIP, cholecystokinin, neuropeptide Y.
- Other small peptides act in a paracrine fashion as diffusible hormones that affect many neurones over great distance (neurohormones like endorphins and enkephalins – natural painkillers).
- The pain pathway starts at nociceptors and is transmitted via sensory nerves, the spinal cord, eventually to be perceived in the brain (Fig. 11.1):
 - nociceptors
 - dorsal horn
 - midbrain
 - thalamus and hypothalamus
 - cerebral cortex (somatosensory and limbic).
- Perception is critical to sensing pain. Modulation, either enhancing or inhibiting nociception, is also crucial

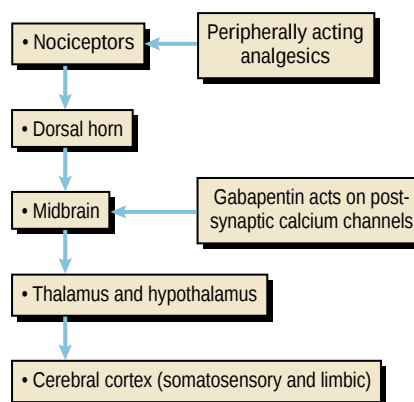


Fig. 11.1 Pain pathway modulation by peripherally acting analgesics and gabapentin

to pain perception. Analgesics can block at various points in this pathway.

Most pain management techniques probably mimic endogenous pain inhibition processes. A person's emotions are an important source for pain modulation. Pain that is difficult to relieve probably results from enhanced nociceptive signals, sometimes fuelled by the person's emotional state.

Headaches

Headaches may have an obvious, but unimportant cause (e.g. hangovers). Most recurrent headaches (tension-type, migraine and cluster headaches) and most orofacial pain is not life threatening, but these conditions can interfere with the quality and enjoyment of life. Most acute head pain has a simple cause and there are no serious sequelae but some, such as an acute ('thunderclap') headache or progressive subacute headache may have sinister implications and can be life threatening, such as an intracranial haemorrhage or meningitis, and warrants urgent investigation. Any patient older than 50 years who develops headaches for the first time or who has a change in a chronic headache pattern should be investigated for an underlying cause. One of these, giant cell arteritis, needs to be recognized and treated promptly with corticosteroids to avoid loss of vision. Other causes of headache that are more common in older people include subdural haematomas, herpes zoster infection, malignancies and trigeminal neuralgia (Chapter 38).

Orofacial pain

Most orofacial pain – probably over 95% – arises from diseases of the teeth and is thus termed 'odontogenic' (Fig. 11.2). There are also non-odontogenic causes; these



Fig. 11.2 Dental abscess; odontogenic causes are the main reasons for orofacial pain

can be of organic origin (neurological or vascular) or non-organic (functional or psychogenic).

Diagnosis

The most important means of diagnosis of orofacial pain is the history. In order to differentiate the widely disparate causes, it is essential to determine key points about the pain (**Box 11.1**):

- **Location:** valuable information can be obtained by watching the patient when asked if the pain is localized or diffuse. For example, patients frequently point with one finger when describing trigeminal neuralgia, but atypical facial pain is much more diffuse and may radiate.

➤ Box 11.1

More comprehensive list of causes of orofacial pain

Local disorders

- Teeth and supporting tissues
- Jaws
- Maxillary antrum
- Salivary glands
- Nose and pharynx
- Eyes

Neurological disorders

- Idiopathic trigeminal neuralgia
- Malignant neoplasms involving the trigeminal nerve
- Glossopharyngeal neuralgia
- Herpes zoster (including postherpetic neuralgia)
- Multiple sclerosis
- SUNCT (severe unilateral neuralgia and conjunctival tearing) syndrome

Possible psychogenic causes

- Atypical facial pain
- Burning mouth syndrome
- Temporomandibular pain–dysfunction

Vascular disorders

- Migraine
- Migrainous neuralgia
- Giant cell arteritis
- Paroxysmal hemicrania
- Neuralgia-inducing cavitational osteonecrosis (NICO)

Referred pain

- Nasopharyngeal
- Ocular
- Aural
- Cardiorespiratory
- Angina
- Lesions in the neck or chest (including lung cancer)

- **Character:** patients should be asked about the severity and whether the pain is 'sharp', 'dull', 'aching', 'throbbing' or 'shooting'. Ask the patient to rate the pain severity on a scale of zero (no pain) to 10 (most severe pain that the patient has experienced), or ask them to mark this on a line divided into 10 equal sections (visual analogue scale) or use an assessment instrument such as the McGill pain questionnaire. These help assess the severity, accepting always that it is subjective, and may also be useful in monitoring the response to treatment. Disturbance of the normal sleep pattern by pain is also useful in assessing the severity.
- **Duration:** the average duration of each episode may help diagnosis. For example, pain from exposed dentine is fairly transient, lasting only for seconds, while the pain from pulpitis lasts for a longer period. Trigeminal neuralgia is a brief lancinating pain lasting up to about 5 seconds, migrainous neuralgia lasts 30–45 minutes, migraine lasts hours or days, while atypical facial pain is persistent.
- **Frequency and periodicity:** determine whether the pain occurs at specific times. A pain diary can help. For example, the pain of sinusitis is often aggravated by lying down, while periodic migrainous neuralgia frequently disturbs the patient's sleep at a specific time each night, around 2.00 a.m. The pain of temporomandibular joint pain-dysfunction syndrome may be more severe on waking.
- **Precipitating, aggravating and relieving factors:** ask if any factors influence the pain. For example, temperature often aggravates dental pain, touching a trigger zone may precipitate trigeminal neuralgia attacks, stress may worsen atypical facial pain, and alcohol may induce migrainous neuralgia episodes. It may be necessary to resort to leading questions, asking about the effects of temperature, biting, posture, analgesics, alcohol, etc.
- **Associated features:** some types of pain may be associated with other features that are helpful diagnostically. These include a swollen face in dental abscess, nausea and vomiting in migraine, or a history of nasal stuffiness or lacrimation in migrainous neuralgia.

Thus, the answers to a series of features may be needed, including:

- Previous history.
- Character:
 - continuous
 - very severe
 - dull
 - throbbing
 - lancinating
 - burning sensation
 - interferes with sleep.
- Provoking or relieving factors:
 - worse with hot/cold
 - worse on biting
 - worse with exercise
 - worse on moving head
 - trigger point
 - other provoking factors known
 - stress related
 - alcohol changes pain.
- Other features:
 - ocular or nasal symptoms
 - neurological signs or symptoms
 - nausea/vomiting
 - relieved by analgesics/drugs
 - weight loss
 - temporomandibular click
 - trismus.

Various instruments, such as IMPATH and the TMJ Scale, are available to assess behavioural and psychological factors.

Local causes of orofacial pain

Most orofacial pain is related to dental disease – odontogenic causes.

Dentinal pain

Pain originating in dentine:

- is sharp and deep
- is usually evoked by an external stimulus (normally food and drinks which are hot, cold, sweet, sour or, sometimes, salty). Although extreme changes in temperature (e.g. hot soup followed by ice-cream) may cause pain in intact, non-diseased teeth, pain evoked by natural stimuli usually indicates a hyperalgesic state of the tooth
- usually subsides within a few seconds of withdrawal of stimulus
- may be poorly localized, often only to an approximate area within two to three teeth adjacent to the affected tooth. Sometimes, the patient is unable to distinguish whether the pain originates from the lower or the upper jaw. Pain from affected posterior teeth is more difficult to localize than that from anterior teeth. However, patients rarely make localization errors across the midline.

Pulpal pain

Vitalometry using a pulp vitality tester may be indicated. Pain associated with pulp disease:

- is spontaneous. Pain may be described by patients in different ways, and a continuous dull ache can

periodically be exacerbated (by stimulation or spontaneously) for short (minutes) or long (hours) periods. The pain of pulpitis is frequently discontinuous and abates spontaneously; the precise explanation for such abatement is not clear

- is strong, and can be excruciating for many minutes
- is often throbbing
- is typically exacerbated by temperature change and pressure on a carious lesion
- may increase and throb when the patient lies down, and in many instances wakes the patient from sleep
- outlasts the stimulus (unlike stimulus-induced dental pain)
- is poorly localized, particularly when pain becomes more intense
- tends to radiate or refer to the ipsilateral ear, temple and cheek, but does not cross the midline.

Periodontal pain

Pain originating in the periodontium:

- is more readily localized than is pulpal pain. The improved ability to localize the source of pain may be attributed to the proprioceptive and mechanoreceptive sensibility of the periodontium that is lacking in the pulp. However, although localization of the affected tooth is often precise, in up to half of cases the pain is diffuse and radiates into the jaw on the affected side
- may be less severe than pulpal pain
- is often associated with tenderness to pressure on the affected teeth
- is usually not aggravated by heat or cold.

Acute periapical periodontitis

Pain associated with acute periapical inflammation:

- is spontaneous in onset
- is moderate to severe in intensity
- persists for long periods of time (hours)
- is exacerbated by biting on the tooth and, in more advanced cases, even by closing the mouth and bringing the affected tooth gently into contact with the opposing teeth. In these cases, the tooth feels 'high' (extruded) and is very sensitive to touch
- has often been preceded by pulpal pain
- is usually better tolerated than the paroxysmal and excruciating pain of pulpitis
- is usually precisely localized and the patient is able to indicate the affected tooth. During examination the affected tooth is located readily by means of tooth percussion
- is usually associated with a non-vital tooth

- is usually associated with tenderness to palpation in the periapical buccal vestibular area
- may be associated with swelling of the face, caused by oedema and cellulitis or sometimes connected with fever and malaise. Usually, when the face swells, pain diminishes in intensity due to rupture of the pus through the periosteum of the bone around the affected tooth and the consequent decrease in pressure of the tooth apex.

Lateral periodontal abscess

- The pain is similar to that of acute periapical periodontitis, though often less severe, and is well localized and with swelling and redness of the gingiva.
- However, the swelling is usually located more gingivally than in the case of an acute periapical lesion.
- The affected tooth is sensitive to percussion and is often mobile and slightly extruded, and there is a deep periodontal pocket. Probing the pocket may cause pus exudation and subsequent relief from pain.
- The tooth pulp is usually vital.

Food impaction

The cause of food impaction is usually a faulty contact between the teeth because of caries or poor restorations. Examination shows a faulty contact between two teeth and often food trapped between these teeth; the gingival papilla is tender to touch and bleeds easily.

Food impaction interdentally can cause:

- localized pain that develops between or in two adjacent teeth after meals, especially when food is fibrous (e.g. meat)
- pain associated with a feeling of pressure and discomfort, which may gradually disappear until being evoked again at the next meal, or may be relieved immediately by removing the impacted food
- the adjacent teeth to be sensitive to percussion
- oral malodour.

Cracked tooth

Examination may fail to elicit the cause of pain. Cracks may be revealed by biting on rubber or a Tooth Slooth or Fracfinder, by fibre-optic or blue light illumination or by staining with, for example, disclosing solution. Teeth can crack under trauma and can give rise to pain which is:

- severe
- worse on biting
- often precipitated by hot or cold.

Pericoronitis

Acute pericoronal infections are common, and are related to incompletely erupted teeth partially covered by flaps of gingival tissue (operculum), particularly lower third molars. Pain is spontaneous and is often exacerbated by closing the mouth. In more severe cases, pain may be aggravated by swallowing, and there may be trismus and, occasionally, fever, lymphadenopathy and malaise. Examination shows an operculum that is acutely inflamed, red and oedematous. Frequently, an opposing upper tooth indents or ulcerates the oedematous operculum.

Acute necrotizing gingivitis

Examination shows necrosis and ulceration of the gingival papilla with different degrees of marginal gingival destruction. Similar features but with more intense pain may be seen in necrotizing periodontitis in HIV/AIDS. Acute necrotizing gingivitis may cause:

- soreness and pain. In the early stages some patients may complain of a feeling of tightness around the teeth. Pain is fairly well localized to the affected areas
- profuse gingival bleeding
- halitosis, usually
- metallic taste, sometimes
- fever and malaise, sometimes.

Mucosal pain

Pain from oral mucosal lesions can be either localized or diffuse. Localized pain is usually associated with an erosion or ulcer. Diffuse pain may be associated with a widespread infection, mucosal atrophy or erosion, a systemic underlying deficiency disease or other factors, and is usually described as 'soreness' or sometimes 'burning'. Mucosal pain may be aggravated mechanically by touch, or by sour, spicy, salty or hot foods.

Other local causes of orofacial pain

Jaws

Pain from the jaws can be caused by acute infection, malignancies, Paget's disease and direct trauma. Lesions such as cysts, retained roots and impacted teeth are usually painless unless associated with infection or fracture of the jaw. Odontogenic and other benign tumours of the bone do not normally produce pain, but malignant tumours usually produce deep, boring pain, sometimes associated with paraesthesia, hypoaesthesia or

anaesthesia. Radiation therapy or bisphosphonate may result in severe pain due to infection associated with osteonecrosis.

Temporomandibular joint

Pain from the temporomandibular joint may result from dysfunction, trauma, acute or chronic inflammation, or primary or secondary malignant tumours. Examination may reveal the masticatory muscles tender to palpation or occasionally the joint swollen and warm to touch or tender to palpation via the external auditory meatus. Pain from the temporomandibular joint:

- is usually dull
- is usually caused by muscle spasm. Nociceptors may be triggered by release of substances such as cytokines (interleukin-1 and IL-6, and tumor necrosis factor), lactic acid, potassium ions, prostaglandin E2, bradykinin, leukotriene B4, serotonin, neuropeptides such as substance P (SP), neuropeptide Y, calcitonin gene-related peptide (CGRP) or somatostatin
- is usually poorly localized
- may radiate widely
- is usually intensified by movement of the mandible
- may be associated with trismus because of the spasm in the masticatory muscles.

Salivary glands

Examination usually reveals the salivary gland swollen and sensitive to palpation. In acute parotitis, mouth-opening causes severe pain, and thus there is a degree of trismus. Salivary flow from the affected gland is usually reduced. Pain may be associated with fever and malaise. In children, the most common cause is mumps. In adults, pain from salivary glands results usually from blockage of a salivary duct by calculus or a mucus plug, or sialadenitis, when pus may exude from the duct orifice. Pain from salivary gland disorders:

- is localized to the affected gland
- may be quite severe
- may be intensified by increased salivation, such as before and with meals – the pain may wane in the minutes/hours following such salivary stimulation.

Sinuses and pharynx

Disease of the paranasal sinuses and nasopharynx can cause oral and/or facial pain. In acute sinusitis there has usually been a preceding 'cold' followed by local pain and tenderness (but not swelling) and radio-opacity of the affected sinuses, sometimes with an obvious fluid level. Transillumination from a light in the oral cavity may show a fluid level. With maxillary sinusitis, pain may be felt in related upper molars and premolars, any of which may be tender to percussion. The pain of ethmoidal or sphenoidal sinusitis is deep in the nose. Pain

in any type of acute sinusitis may be aggravated by a change of position of the head.

Tumours of the sinuses or nasopharynx can also cause facial pain. These tumours are often carcinomas that infiltrate various branches of the trigeminal nerve and can remain undetected until too late. Nasopharyngeal carcinoma often presents late, with facial pain, paraesthesia, ipsilateral deafness and/or cervical lymph node enlargement (Trotter syndrome).

Pressure on the mental nerve

Rarely, pain is caused by pressure from a denture on the nerve, which comes to lie on the crest of the ridge as the alveolar bone is resorbed in the edentulous mandible. Either the denture should be relieved from the area or, occasionally, it is necessary to re-site the nerve surgically.

Neurological (neuropathic) causes of orofacial pain

Sensory innervation of the mouth, face and scalp depends on the trigeminal nerve, so that disease affecting this nerve can cause orofacial pain or, indeed, sensory loss – sometimes with serious implications.

Facial neuralgia caused by tumours or other lesions

Any lesion affecting the trigeminal nerve, whether it be traumatic, cerebrovascular disease, multiple sclerosis, infections such as HIV/AIDS, inflammatory or neoplastic (e.g. a nasopharyngeal or antral carcinoma), may cause pain, often with physical signs, such as facial sensory or motor impairment.

Idiopathic trigeminal neuralgia

Severe lancinating unilateral orofacial pain may be of idiopathic origin, and in the absence of identifiable organic cause is termed 'idiopathic trigeminal neuralgia' (see Ch. 36). Similar pain is experienced in the rare idiopathic short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing (abbreviated to SUNCT syndrome).

Other neuralgias

Glossopharyngeal and postherpetic neuralgias may also cause pain.

Vascular causes of orofacial pain

Several disorders in which the most obvious organic feature is vascular dilatation or constriction cause orofacial pain. The pain is usually obviously in the face or head rather than in the mouth, but occasionally can involve both, and can be difficult to differentiate from other causes of orofacial pain (Table 11.1). These include:

- migraine
- migrainous neuralgia
- giant cell arteritis.

A rare condition termed neuralgia-inducing cavitation osteonecrosis (abbreviated to NICO), related to disorders in blood coagulation, may also cause jaw pain.

Other organic causes of headache or orofacial pain

Headache or orofacial pain is occasionally the presenting feature of:

- exertion (including postcoital headache)
- fevers
- hypertension
- meningeal irritation: severe headache with nausea, vomiting, neck pain or stiffness (with inability to kiss the knees) or pain on raising the straightened legs (Kernig sign) implies meningeal irritation. Urgent neurological attention is needed, since the pain may indicate meningitis, metastases or subarachnoid haemorrhage
- raised intracranial pressure: this is one of the most serious, but also the least common causes of headache. The headache is severe, worse on waking and decreases during the day. It is aggravated by straining, coughing, sneezing or lying down. Nausea and vomiting are common. Neurological attention and examination for papilloedema is essential, since this may be caused by malignant hypertension, a tumour, abscess or haematoma. When no specific cause can be found it is termed 'idiopathic ('benign') intracranial hypertension', which may be precipitated by tetracyclines, vitamin A, nitrofurantoin and nalidixic acid and is associated with partial thrombosis of the superior sagittal sinus
- chronic obstructive airways disease
- some endocrinopathies, such as diabetes
- HIV infection
- drug use (e.g. nitrites, phenothiazines)
- Paget's disease.

Table 11.1
Differential diagnosis of orofacial pain

	Dental	Periodontal	Mucosal	Salivary glands	Neuralgic	Vascular	TMJ pain-dysfunction
Location	Mouth, ear, jaws, cheek	Tooth	Mucosa	Area of gland	Nerve distribution	Orbit or upper face	Temple, ear, jaws, teeth
	Poor, diffuse, radiating, does not cross midline	Good	Usually good	Usually good	Good	Usually good	Poor, but usually unilateral
Duration	Seconds to days	Hours to days	Hours to days	Hours to days	Seconds	Minutes to hours	Weeks to years
Character	Intermittent, sharp, paroxysmal	Steady, boring	Burning or sharp	Drawing, pulling	Lancinating, paroxysmal	Throbbing, deep	Dull, continuous
Precipitants	Hot and cold	Chewing	Sour and spicy foods	Eating	Touch, wind	Alcohol	Yawning, chewing
Associated features	Caries, exposed dentine	Advanced periodontitis	Abscess, erosions or ulcers	Salivary gland swelling	None usually	Lacrimation, injected eye, nasal discharge	Click in TMJ, trismus
Aetiology	Caries, trauma, gingival recession	Acute periodontitis	Varied	Saliva retention, infection	Idiopathic, multiple sclerosis	Vasomotor	Stress, parafunction
Treatment	Cracked tooth, restoration, endodontics	Endodontics, periodontics or extraction	According to cause	Drainage, antibiotics	Carbamazepine, nerve block, cryoanalgesia, neurosurgery	Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan or zolmitriptan) or clonidine, methysergide or lithium carbonate	Antidepressants, other treatments

Chronic post-traumatic headache

Most persons who have had head injuries have local pain or tenderness at the site of impact for a few hours or even for a few days, after which many become symptom-free. However, up to one-half of all persons who injure their heads sufficiently to warrant hospitalization develop chronic post-traumatic headaches. A small number of patients with headaches that persist after head injury have pain due to bleeding in the epidural, subdural or subarachnoid spaces, which is potentially lethal and needs urgent neurological attention. The headache of subdural haematoma begins at the time of trauma or the regaining of consciousness and persists, often for weeks or months, until the haematoma is removed. Blood in the subarachnoid space may induce headache, as may adhesions after

head injury involving pain-sensitive structures in the arachnoid. However, most patients with post-traumatic headaches that persist or recur for long periods after head injury have no identifiable intracranial abnormalities to explain their pain and some of these have a 'compensation neurosis' – a psychogenic type of pain.

Causalgia

Causalgia is a persistent burning pain, often in the mandible, that follows surgery or trauma. The cause is unclear and there is no good evidence that it is related to a peripheral nerve lesion or to psychogenic causes.

If a local anaesthetic injection relieves causalgia then cryoanalgesia may effect relief, but neurosurgery may be required.

Frey syndrome

Frey syndrome (auriculotemporal syndrome, see Ch. 37) is a paroxysmal burning pain, usually in the temporal area or in front of the ear, associated with flushing and sweating on eating, which often follows parotid surgery and appears to be due to abnormal reinnervation.

Functional causes of orofacial pain

The mouth and perioral soft tissues have among the richest sensory innervation in the body. Furthermore, a large part of the sensory homunculus on the cerebral cortex receives information from orofacial structures. Right from infancy, the mouth is concerned intimately with the psychological development of the individual, and disorders of structures, such as the lips, teeth and oral mucosa can hold enormous emotional significance. It is hardly surprising, therefore, that there are a range of psychogenic types of orofacial pain.

In some studies, nearly 40% of the population have reported frequent headaches and orofacial pain. Four main groups of patients appear to suffer from functional (psychogenic) pain:

- Normal individuals under extreme stress
- Those with a personality trait, such as hypochondriasis
- Neurotic, often depressed persons
- Rarely, psychotic patients.

Features common to most conditions with a psychogenic component, sometimes termed 'medically unexplained symptoms' (MUS), include the following:

- Many are female
- Constant chronic discomfort or pain
- Pain often of a dull boring or burning type
- Pain that is poorly localized (it may cross the mid-line to involve the other side or may move elsewhere)
- Pain that rarely wakens the patient from sleep; however, sleep disturbances are common

- Total lack of objective signs of organic disease
- All investigations are also negative
- There are often recent adverse 'life events', such as bereavement or family illness
- There are often multiple oral and/or other MUS, such as headaches, chronic back or neck pain, irritable bowel syndrome, insomnia, numbness or dysmenorrhoea (Table 11.2).
- Cure is uncommon in most, yet few of those suffering seem to try or persist in using analgesics.

The reasons for MUS may include the following:

- Possible links between neurohumoral mechanisms and altered CNS function
- The heightening of bodily sensations (lowered pain threshold) as a consequence of physiological processes, such as autonomic arousal, muscle tension, hyperventilation or inactivity
- Misattribution of normal sensations to serious physical disorders.

Psychogenic (tension) headaches are common, especially in young adults. The headache, which is caused by anxiety or stress-induced muscle tension, affects the frontal, occipital and/or temporal muscles, and is felt as a constant ache or band-like pressure. The pain is often worse by the evening, but does not waken the patient. Reassurance may be effective, but the pain may be helped by massage, warmth, non-steroidal anti-inflammatory drugs (NSAIDs), or benzodiazepines, such as diazepam, as this is both anxiolytic and a mild muscle relaxant.

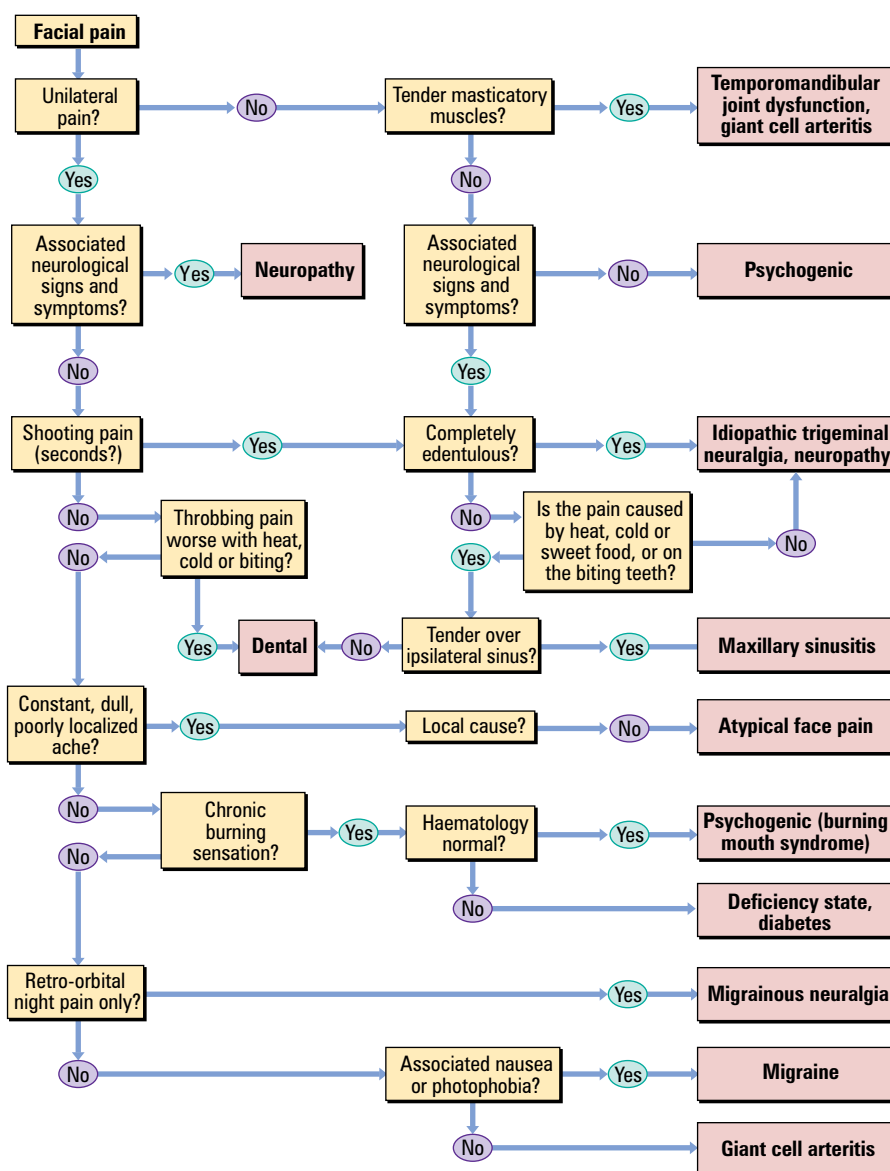
The most common types of orofacial pain with a strong psychogenic component are:

- atypical facial pain
- oral dysaesthesia (burning mouth syndrome)
- temporomandibular pain-dysfunction
- atypical odontalgia
- the syndrome of oral complaints.

Multiple pains and other complaints may occur simultaneously or sequentially and relief is rarely found (or admitted). Patients may bring diaries of their symptoms to emphasize their problem. Some have termed this the 'malady of small bits of paper' (*la maladie du petit*

Table 11.2
Medically unexplained symptoms – pain at various sites

System	Comments
Chest	Tietze syndrome
Gastrointestinal	Irritable bowel syndrome
Musculoskeletal	Low back pain
Ear, nose, throat	Dysphagia (globus hystericus)



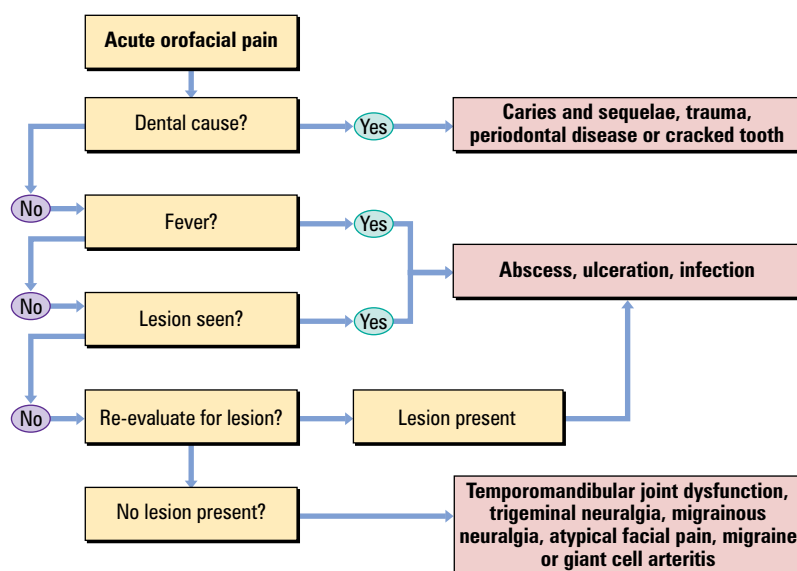
Algorithm 11.1 Facial pain

papier) and, though there is not always a psychogenic basis, such notes characterize patients with non-organic complaints. An anecdotal example is a 35-year-old woman who sequentially 'developed' right submandibular gland pain, right glossopharyngeal neuralgia (her words!), left glossopharyngeal neuralgia and left submandibular pain over a period of 15 years, during which time she appeared not to develop signs of neurological disease or to deteriorate physically. On the other hand, written notes kept by the patient can be of considerable help to the clinician. Occasional patients quite deliberately induce painful oral lesions and some have Munchausen syndrome, where they behave in such a fashion as to appear to want operative intervention.

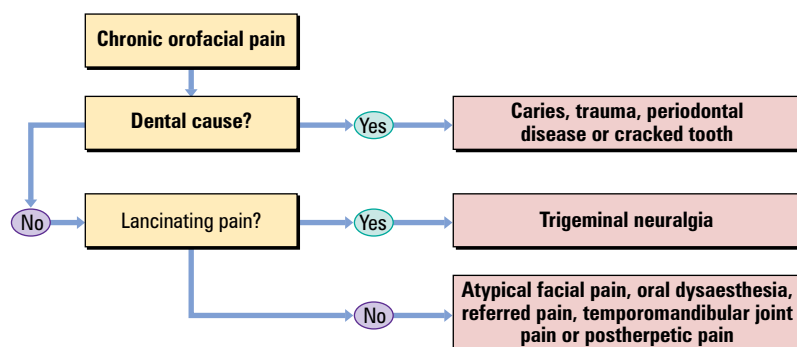
Referred causes of orofacial pain

Pain may occasionally be referred to the mouth, face or jaws from the following:

- Neck: cervical vertebral disease, especially cervical spondylosis, very occasionally causes pain referred to the face.
- Heart, in patients with angina: the latter pain usually affects the mandible, is initiated by exercise (especially in the cold) and abates quickly on rest.



Algorithm 11.2 Acute facial pain



Algorithm 11.3 Chronic facial pain

- Lungs: orofacial pain emanating from lung cancer is a well-recognized entity and has been misdiagnosed as temporomandibular joint pain.
- Oesophagus: pain plus sialorrhoea may result from oesophageal lesions.
- Styloid process (stylalgia): eagle syndrome, a rare disorder due to an elongated styloid process, may cause pain on chewing, swallowing or turning the head.
- Eyes: pain from the eyes can arise from disorders of refraction, retrobulbar neuritis (e.g. in multiple sclerosis), or glaucoma (raised intraocular pressure), and can radiate to the orbit or frontal region.
- Ears: middle-ear disease may cause headaches. Conversely, oral disease not infrequently causes pain referred to the ear, particularly from lesions of the posterior tongue. The classic picture is an elderly man with an undiagnosed tongue cancer who complains of earache.
- Pharynx: carcinoma of the pharynx may cause facial pain.

Diagnosis of orofacial pain

The cause of orofacial pain is established mainly from the history and examination findings, but it is important to consider the usefulness of additional investigations, particularly imaging of the head and neck, using CT or MRI (Algorithms 11.1–11.3). It is important not to miss detecting organic disease and thus mislabelling the patient as having psychogenic pain (Tables 11.2–11.4). Even patients with psychogenic disorders can suffer organic pain.

Management of orofacial pain

Pain is the most important symptom suggestive of oral disease, but absence of pain does not exclude organic disease and presence of pain does not necessarily mean

Table 11.3
Differential diagnosis of oral pain

Source of pain	Character	Exacerbating factors	Ability to locate signs	Associated with	Pain provoked by	Radiography
<i>Dental</i>						
Dentinal	Evoked, does not outlast	Hot/cold, sweet/sour	Poor	Caries, defective restorations, exposed dentine	Hot/cold, probing dentine	May show interproximal caries, defective restorations
Pulpal	Severe, intermittent, throbbing	Hot/cold, sometimes biting	Poor	Deep caries, extensive restoration	Hot/cold, probing, sometimes percussion	May show deep caries or deep restoration
<i>Periodontal</i>						
Periapical	For hours at same intensity; deep, boring	Biting	Good	Periapical swelling and redness, tooth mobility	Percussion, palpation of periapical area	Periapical views may show periapical changes
Lateral	For hours at same level, boring	Biting	Good	Periodontal, boring, deep pockets with pus exuding, tooth mobility	Percussion, palpation of periodontal area	Useful when X-rayed with probe inserted into pocket
Gingival	Pressing, annoying	Food impaction, toothbrushing	Good	Acute gingival inflammation	Touch, percussion	Not applicable
<i>Mucosal</i>						
Mucosal	Burning, sharp	Sour, sharp and hot food	Good	Erosive or ulcerative lesions, redness	Palpation	Not applicable

Table 11.4
Differentiation of important types of facial pain

	Idiopathic trigeminal neuralgia	Atypical facial pain	Migraine	Migrainous neuralgia
Age (years)	50	30–50	Any	30–50
Sex	F>M	F>M	F>M	M>F
Site	Unilateral, mandible or maxilla	± Bilateral, maxilla	Any, especially supraorbital	Retro-orbital
Associated features	–	± Depression	± Photophobia ± nausea ± vomiting	Conjunctival injection ± lacrimation ± nasal congestion
Character	Lancinating	Dull	Throbbing	Boring
Duration	Brief (seconds)	Continual	Hours (usually daytime)	Few hours (usually night)
Precipitating factors	Trigger areas	None	± Foods	± Alcohol
Relieving factors	Carbamazepine	Antidepressants	Sumatriptan, clonidine; ergot derivatives	Oxygen, sumatriptan, clonidine, ergot derivatives, verapamil

organic disease. There is also considerable individual variation in response to pain, and the threshold is lowered by tiredness, and psychogenic and other factors:

- Simple analgesics, such as NSAIDs, should be used initially, before embarking on more potent preparations. Chronic pain requires regular analgesia (not just as required). Details are given in Chapter 5.
- Antidepressants may help in pain of psychogenic origin.
- Anticonvulsants may help in neuropathic pain (neuralgias).
- Opioids may help in cancer pain.

It is important also:

- where possible, to identify and treat the cause of pain
- to relieve factors that lower the pain threshold (fatigue, anxiety and depression)
- to avoid polypharmacy.

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12

Red, white and pigmented lesions

Key points

Main causes of oral red lesions:

- Inflammatory
- Reactive
- Erosive
- Atrophic
- Purpura
- Vascular
- Neoplasms

Main causes of white oral lesions:

- Leukoedema
- Local causes
- Inherited (e.g. white sponge naevus)
- Leukoplakia
- Neoplasms
- Infections
- Mucocutaneous disease

Main causes of pigmented mucosal lesions:

- Increased melanin:
 - racial
 - ephelis (freckle)
 - pigmentary incontinence
 - melanotic macules
 - naevus
 - malignant melanoma
 - Peutz–Jeghers syndrome
 - Addison's disease (and related disorders)
- Exogenous pigments:
 - amalgam or graphite tattoo
 - habits and drugs
 - heavy metals

and signify severe dysplasia or malignant neoplasms. Red lesions can be:

- *Focal*: the lesion of most concern is erythroplasia, since it is usually dysplastic. Telangiectasia can also cause red lesions.
- *Multifocal*: these lesions are often caused by candidiasis.
- *Discoid*: these are prominent on the tongue in erythema migrans (geographic tongue).
- *Diffuse*: these lesions may be caused by mucositis, deficiency states and many infections, but candidiasis is the most common cause.
- *Linear*: these may be seen on the tongue in deficiency states.

Causes of red oral lesions

Mucosal inflammation

Most red lesions are inflammatory. The most common are (Box 12.1):

- viral stomatitis: erythema is seen with most oral viral infections (e.g. herpes simplex stomatitis)
- candidiasis:
 - denture-related stomatitis is a form of mild chronic atrophic candidiasis consisting of inflammation of the mucosa beneath a denture (usually a complete upper denture), such that the hard palate is red (Fig. 12.1)
 - acute oral candidiasis may complicate corticosteroid or antibiotic therapy, particularly with long-term, broad-spectrum antimicrobials, and causes widespread erythema and soreness of the oral mucosa, sometimes with thrush
 - erythematous oral candidiasis may complicate HIV disease, and causes focal or widespread erythema and soreness of the oral mucosa, often in the palate, and sometimes with thrush
 - median rhomboid glossitis is usually detected by the patient or dentist as a persistent red, rhomboidal depapillated area in the midline of the dorsum of the tongue
- deep mycoses, which are rare in the developed world, except in HIV disease and other immunocompromised persons:
 - histoplasmosis
 - cryptococcosis
 - blastomycosis
 - paracoccidioidomycosis

Red lesions

Red oral lesions

These are commonplace and usually caused by inflammation in, for example, mucosal infections, such as candidiasis (Fig. 12.1). However, they can also be sinister



Fig. 12.1 Denture-related stomatitis; red lesions are usually inflammatory in origin, but erythroplasia must be excluded, since it is potentially malignant

► Box 12.1

More comprehensive list of causes of red lesions

Localized

- Inflammatory
- Candidiasis
- Other mycoses
- Reiter's disease
- Graft-versus-host disease
- Drugs
- Epithelioid angiomatosis
- Reactive lesions:
 - pyogenic granulomas
 - peripheral giant cell granulomas
- Atrophic
- Geographic tongue
- Lichen planus
- Lupus erythematosus
- Erythroplasia
- Avitaminosis B₁₂
- Burns
- Vascular
- Purpura
- Telangiectases (hereditary haemorrhagic telangiectasia or scleroderma)
- Angiokeratomas (Fabry's disease)
- Angiomas
- Neoplasms
- Giant cell tumour
- Squamous carcinoma
- Kaposi sarcoma
- Wegener's granulomatosis

Generalized

- Candidiasis
- Avitaminosis B complex (rarely)
- Irradiation or chemotherapy-induced mucositis
- Polycythaemia

- radiation induced mucositis (mucosal barrier injury or MBI) is common after irradiation of tumours of the head and neck, if the radiation field involves the oral mucosa. Arising within 3 weeks of the irradiation, there is generalized erythema, and sometimes ulceration
- chemotherapy induced mucositis is common after chemotherapy. Fluorouracil and cisplatin almost always cause mucositis. Etoposide, melphalan, doxorubicin, vinblastine, taxanes and methotrexate are also particularly stomatotoxic. Arising within 1–2 weeks of the therapy, there is generalized erythema, and sometimes ulceration
- immunological reactions, such as plasma cell gingivostomatitis, granulomatous disorders (sarcoidosis, Crohn's disease, orofacial granulomatosis), amyloidosis and graft-versus-host disease.

Reactive lesions

These are caused by pyogenic granulomas and peripheral giant cell granulomas.

Erosions

These are caused by burns and vesiculobullous disorders such as lichen planus, erythema multiforme, pemphigoid and pemphigus.

Atrophy

These are caused by:

- erythroplasia – one of the more important causes of a localized red lesion, since it is often dysplastic
- erythema migrans – manifests with irregular depapillated red areas, which change in size and shape, usually in the dorsum of the tongue
- lichen planus – may present with atrophic red areas in some forms
- desquamative gingivitis (see Ch. 39) – is a frequent cause of red gingivae, almost invariably caused by lichen planus or pemphigoid
- iron or vitamin deficiency states – may cause glossitis or other red lesions.

Purpura

Bleeding into the skin and mucosa is usually caused by (Box 12.2):

- trauma: occasional small traumatic petechiae at the occlusal line or elsewhere are seen in otherwise healthy patients (Fig. 12.2)
- suction (e.g. fellatio may produce bruising in the soft palate)
- a blood platelet disorder: red or brown pinpoint lesions (petechiae) or diffuse bruising (ecchymoses) are seen, mainly at sites of trauma, such as at the junction of the hard and soft palate (and often extraorally)

► Box 12.2

Causes of oral purpura

- Trauma
- Suction or trauma from:
 - appliances
 - habits
 - coughing
 - fellatio
 - cunnilingus
 - vomiting
- Platelet disorders
 - autoimmune thrombocytopenia (ITP; idiopathic thrombocytopenic purpura)
 - bone marrow disorders
 - aplastic anaemia
 - leukaemia
 - amyloidosis
 - infections:
 - infectious mononucleosis
 - rubella
 - HIV infection
- Gammopathies
- Localized oral purpura (angina bullosa haemorrhagica)
- Vascular disorders
 - Scurvy
 - Ehlers–Danlos syndrome

- localized oral purpura or angina bullosa haemorrhagica: an idiopathic, fairly common, cause of purpura or blood blisters, seen only in the mouth, pharynx or oesophagus, mainly in the soft palate, in older persons.

Vascular anomalies (angiomas and telangiectasia)

These can be caused by:

- dilated lingual veins (varices): these may be conspicuous in the elderly in the ventrum of the tongue and may cause unnecessary alarm. Similar lesions may be seen in the lip
- haemangiomas: these are usually small isolated developmental anomalies, or hamartomas. Rarely, orofacial angiomas may be part of the Sturge–Weber syndrome (haemangioma with epilepsy and hemiplegia; see Ch. 27)
- telangiectasias (dilated capillaries): these may be seen after irradiation of the mouth and in various systemic disorders, such as hereditary haemorrhagic telangiectasia and systemic sclerosis.

Neoplasms

Red neoplasms include the following:

- Peripheral giant cell tumours
- Angiosarcomas, such as Kaposi sarcoma – a common neoplasm in HIV/AIDS, appears in the mouth as



Fig. 12.2 Petechiae from trauma

red or purplish areas or nodules, especially seen on the palate

- Squamous cell carcinomas
- Wegener's granulomatosis
- Midline granulomas.

Diagnosis

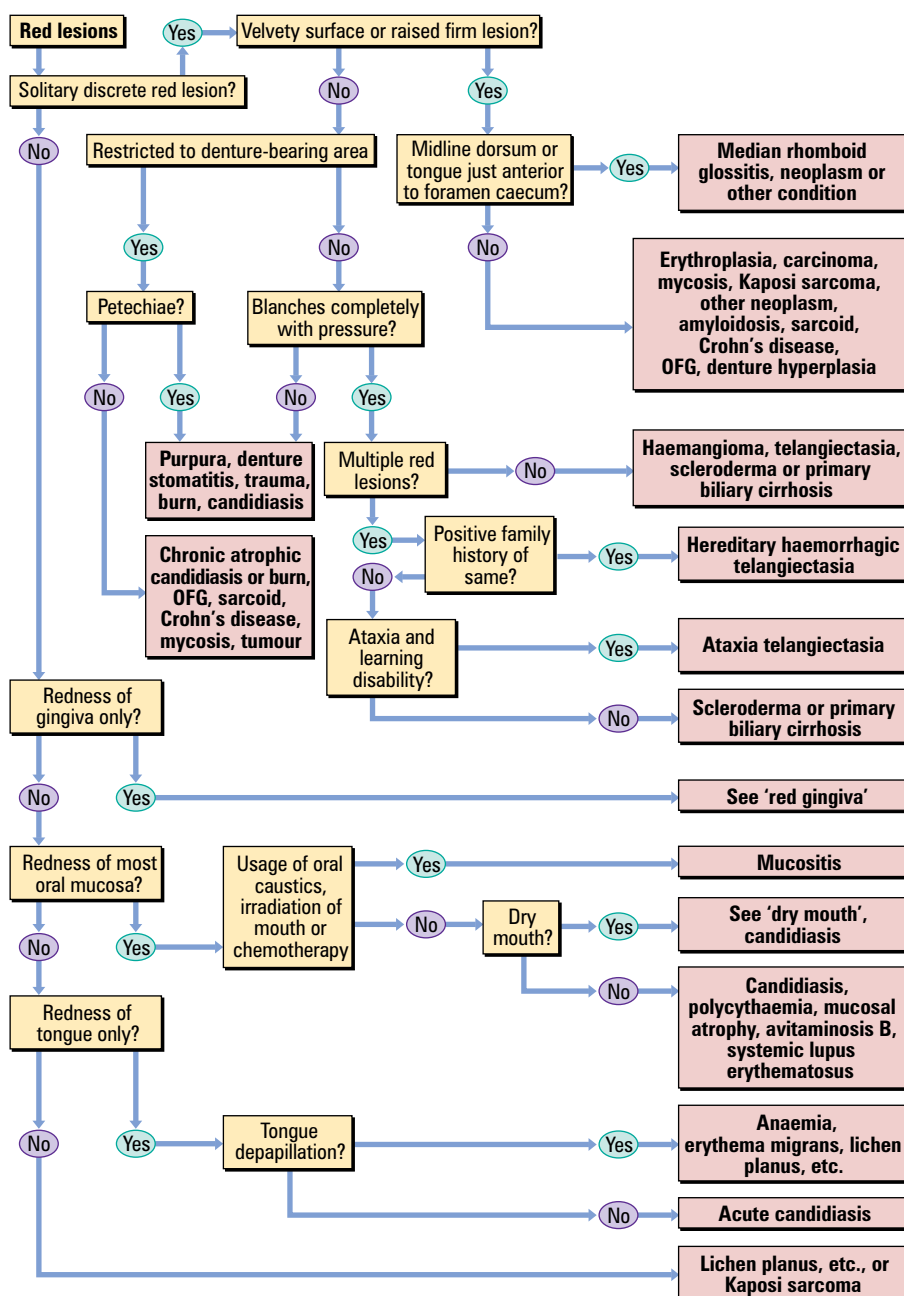
Diagnosis of red lesions is mainly clinical; lesions should also be sought on the skin or other mucosae. Haematological tests and/or biopsy or imaging may be indicated. It may be necessary to take a blood picture (including blood and platelet count) and assess haemostatic function or exclude vitamin deficiencies (Algorithm 12.1).

Management

Treatment is of the underlying cause, usually by excision or laser.

White lesions

Some common conditions, notably Fordyce granules (see Ch. 27) and geographic tongue are yellowish rather than white in colour, but may cause diagnostic confusion. Collections of debris (materia alba) or fungi (candidiasis)



Algorithm 12.1 Red lesions (OFG, orofacial granulomatosis)

may also look white, but these can usually easily be wiped off with a gauze. Other lesions appear white usually because they are composed of thickened keratin, which looks white when wet. These lesions, being inherent in the mucosa, will not easily wipe away with a gauze swab.

White lesions are usually painless, but can be focal, multifocal, striated or diffuse, and these features may give a guide to the diagnosis. For example:

- Focal lesions are often caused by cheek-biting (Fig. 12.3), at the occlusal line (Fig. 12.4), where there are collapsed bullae (Fig. 12.5) or keratosis (Fig. 12.6).
- Multifocal lesions are common in thrush (pseudomembranous candidiasis) and lichen planus.
- Striated lesions are typical of lichen planus.
- Diffuse white areas are seen in the buccal mucosa in leukoedema, and in the palate in stomatitis nicotina.

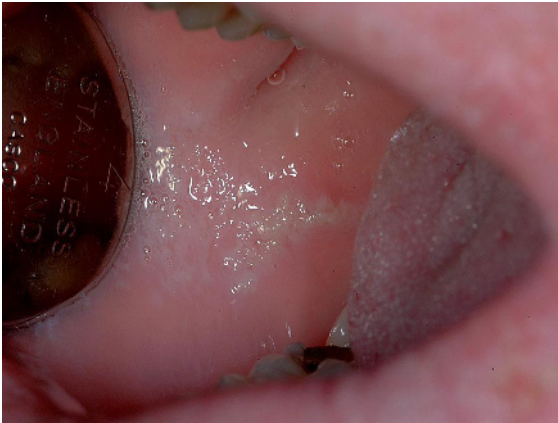


Fig. 12.3 Cheek biting (morsicatio buccarum)



Fig. 12.5 Collapsed bulla



Fig. 12.4 Linea alba (occlusal line)



Fig. 12.6 Keratosis

Main causes of white oral lesions (Box 12.3)

- Leukoedema.
- Local causes:
 - materia alba (debris from poor oral hygiene)
 - keratoses [e.g. frictional keratosis (and cheek/lip biting), smoker's keratosis and snuff-dipper's keratosis]
 - burns
 - grafts
 - scars
 - furred or hairy tongue.
- Inherited (e.g. white sponge naevus).
- Leukoplakia:
 - homogeneous
 - non-homogeneous, either nodular (verrucous) or speckled (erythroleukoplakia).
- Neoplasms:
 - carcinoma
 - verruciform xanthoma.

- Infections:
 - candidiasis (thrush: candidal leukoplakia)
 - Epstein-Barr virus (hairy leukoplakia)
 - human papilloma virus (koilocytic dysplasia, warts, papillomas)
 - syphilis (syphilitic mucous patches and keratosis)
 - measles (Koplik's spots).
- Mucocutaneous disease:
 - lichen planus
 - lupus erythematosus.

Diagnosis

Diagnosis of white lesions is mainly clinical; lesions should also be sought on the skin or other mucosae. Haematological tests and/or biopsy or imaging may be indicated ([Algorithm 12.2](#)).

Management

Treatment is of the underlying cause, or excision.

► Box 12.3

More comprehensive list of causes of oral white lesions

Neoplastic and possibly pre-neoplastic

- Leukoplakia
- Keratoses
- Carcinoma

Inflammatory

- Infective:
 - candidiasis
 - hairy leukoplakia
 - syphilitic mucous patches and keratosis
 - Koplik's spots (measles)
 - some papillomas
 - Reiter's disease
 - koilocytic dysplasia (papilloma virus)
- Non-infective:
 - lichen planus
 - lupus erythematosus

Others

- Cheek-biting
- Materia alba (debris)
- Burns
- Grafts
- Scars
- Verruciform xanthoma

Congenital

- Leukoedema
- Fordyce spots
- White sponge naevus
- Focal palmoplantar and oral mucosa hyperkeratosis syndrome
- Darier's disease
- Pachyonychia congenita
- Dyskeratosis congenita

- Confectionery, such as liquorice.
- Drugs, such as chlorhexidine, iron salts, griseofulvin, crack cocaine, minocycline, bismuth subsalicylate, lansoprazole and HRT.
- Tobacco: this may cause extrinsic discolouration, but can also cause intrinsic pigmentary incontinence, with pigment cells increasing and appearing in the lamina propria. This is especially likely in persons who smoke with the lighted end of the cigarette within the mouth (reverse smoking), as practiced mainly in some Asian communities. Tobacco is a risk factor for cancer.
- Betel: this may cause a brownish-red discolouration, mainly on the teeth and in the buccal mucosa, with an irregular epithelial surface that has a tendency to desquamate. It is seen mainly in women from South and Southeast Asia. Betel chewer's mucosa epithelium is often hyperplastic, and brownish amorphous material from the betel quid may be seen on the epithelial surface and intra- and intercellularly, with ballooning of epithelial cells. Betel chewer's mucosa is not known to be precancerous, but betel use predisposes to submucous fibrosis and to cancer.

Black hairy tongue

This is discussed in Chapter 42.

Intrinsic staining

Increased melanin or number of melanocytes, or other materials can cause intrinsic (endogenous) hyperpigmentation. Intrinsic discolouration may have more significance than the extrinsic type. Normal intrinsic pigmentation is due to melanin, produced by melanocytes – dendritic cells prominent in the basal epithelium. This originates from the amino acid tyrosine, which is converted to dihydroxyphenylalanine (DOPA) and thence to melanin. The colour can vary from brown to blue or black, depending on the amount and location of the melanin. Generalized pigmentation, often affecting the gingivae mainly, is common in persons of colour, and is racial (Figs 12.7 and 12.8).

Localized areas of pigmentation are usually caused by benign conditions:

- Embedded amalgam (amalgam tattoo) (Fig. 12.9)
- Embedded graphite (graphite tattoo)
- Other foreign bodies
- Local irritation/inflammation
- Melanotic macule (Fig. 12.10)
- Naevi
- Melanoacanthoma.

However, neoplasms, such as Kaposi sarcoma or malignant melanoma, are occasionally responsible.

The anterior pituitary gland releases melanocyte stimulating hormone (MSH), which increases melanin production. Melanin pigmentation thus increases under

Hyperpigmentation

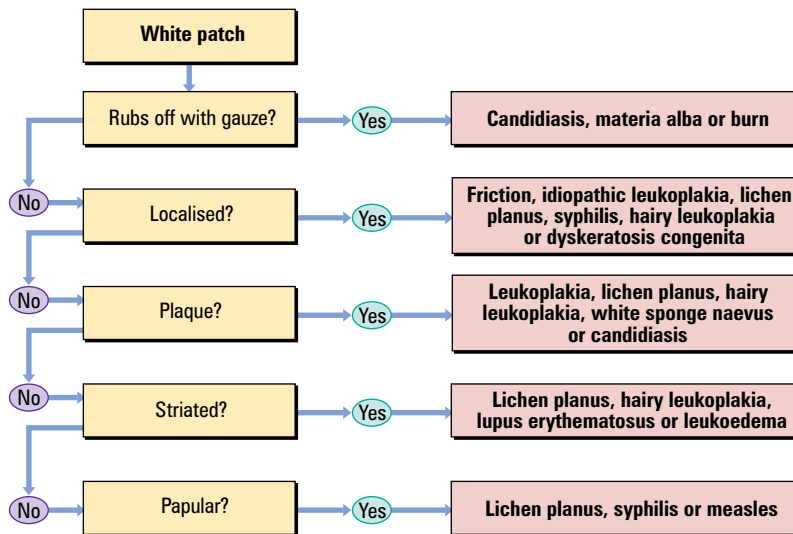
Oral mucosal discolouration, which ranges from brown to black may be due to superficial (extrinsic) or deep (intrinsic in or beneath mucosa) causes.

Types

Extrinsic discolouration

Extrinsic discolouration is rarely of consequence and is usually caused by coloured foods, drinks or drugs. Frequently, both mucosae and teeth are discoloured. Causes include the following:

- Foods and beverages, such as beetroot, red wine, coffee and tea.



Algorithm 12.2 White lesions



Fig. 12.7 Racial pigmentation (the teeth are stained from betel chewing)



Fig. 12.9 Amalgam tattoo

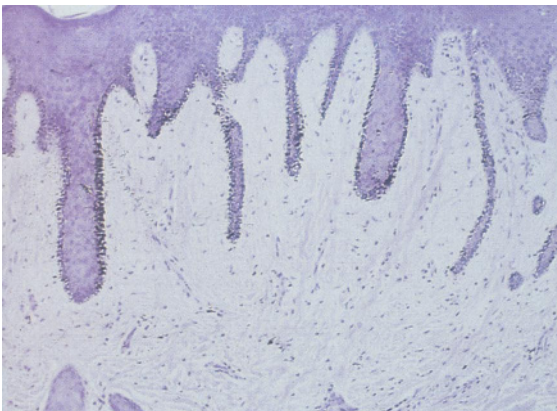


Fig. 12.8 Racial pigmentation



Fig. 12.10 Melanotic macule

hormonal stimulation, either by MSH, or in pregnancy, or rarely due to the action of adrenocorticotrophic hormone (ACTH), the molecule of which is similar to MSH, or under the influence of other factors (e.g. smoking). Thus in all patients systemic causes should be excluded, such as:

- Drugs; including smoking and the contraceptive pill
- Hypoadrenalism; there is increased ACTH production
- Peutz–Jeghers syndrome
- HIV infection
- Von Recklinghausen's disease
- Albright syndrome
- Rarely, palatal pigmentation from bronchogenic carcinoma.

Causes

Causes of oral pigmentation include the following (see Box 12.4):

- Racial pigmentation: this is the most usual cause of patchy or generalized brown oral mucosal pigmentation, caused by melanin. Seen mainly in people of African or Asian heritage it can also be noted in patients of Mediterranean descent, sometimes even in some fairly light-skinned people. It is most obvious in the anterior labial gingivae and palatal mucosa, and the pigmentation is usually symmetrically distributed. Patches may be seen elsewhere. Pigmentation may be first noted by the patient in adult life and then incorrectly assumed to be acquired rather than congenital in origin.
- Chronic inflammation, such as in lichen planus, can result in melanin drop-out, especially in persons with pigmented skin. The oral pigmentation (pigmentary incontinence) is often gingival or buccal.
- Amalgam tattoo: this is the most common cause of a single patch of macular blue-black pigmentation, does not change significantly in size or colour, is painless and is usually seen in the mandibular gingiva or at least close to the teeth or scar of an apicectomy where there has been a retrograde amalgam root-filling.
- Graphite tattoo: this may be seen, for example, where a pencil lead has been broken off in the mucosa. Tattoos are best excised to exclude naevi or melanoma.
- Melanotic macules: these are usually single, brown, collections of melanin-containing cells. Melanotic macules are flat and mostly smaller than 1cm and contain increased melanin, do not change rapidly in size or colour, are painless and are seen particularly on the vermillion border of the lip and on the palate. They are seen mainly in white people and are innocuous. Most arise slowly, but occasionally they rapidly appear. They are best removed to exclude melanoma.
- Naevi: these are blue-black often papular lesions formed from increased melanin-containing cells (naevus cells) and are usually smaller than 1cm. Some 60% are raised, they do not change rapidly in size or colour, are

► Box 12.4

Causes of hyperpigmentation

Localized

- Amalgam, graphite, carbon, dyes, inks or other tattoos
- Ephelis (freckle)
- Epithelioid angiomatosis
- Kaposi's sarcoma
- Malignant melanoma
- Melanoacanthoma
- Melanotic macule
- Naevus
- Pigmented neuroectodermal tumour
- Verruciform xanthoma

Multiple or generalized

- Genetic:
 - racial
 - Carney syndrome (Ch. 43)
 - complex of myxomas, spotty pigmentation and endocrine overactivity
 - Laugier–Hunziker syndrome (Ch. 43)
 - lentiginosis profusa
 - leopard syndrome (Ch. 43)
 - Peutz–Jeghers syndrome
- Drugs:
 - ACTH
 - amiodarone
 - antimalarials
 - betel
 - busulphan
 - chlorpromazine
 - clofazamine
 - contraceptive pill
 - ketoconazole
 - menthol
 - metals (bismuth, mercury, silver, gold, arsenic, copper, chromium, cobalt, manganese)
 - methyldopa
 - minocycline
 - phenothiazines
 - smoking
 - zidovudine
- Endocrine:
 - Addison's disease
 - Albright's syndrome
 - Nelson's syndrome
 - pregnancy
- Post-inflammatory
- Others:
 - Gaucher's disease
 - generalized neurofibromatosis
 - haemochromatosis
 - HIV disease
 - incontinentia pigmenti
 - thalassaemia
 - Whipple's disease
 - Wilson's disease

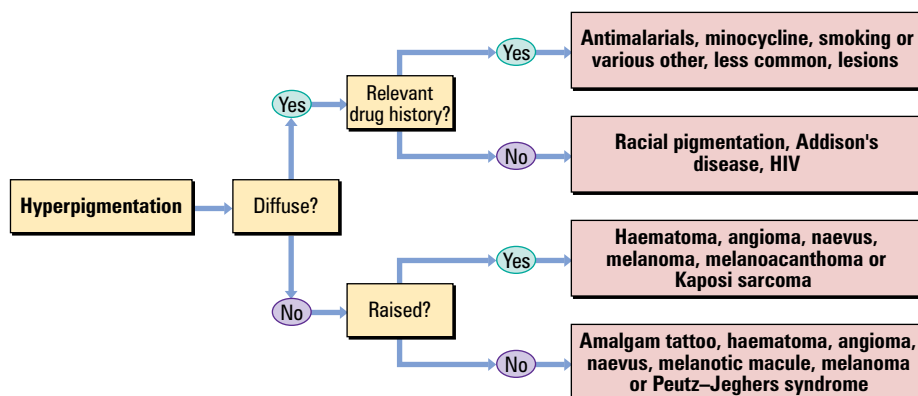
painless and are seen particularly on the palate. Approximately half of naevi are histologically of the intra-dermal (intramucosal) type when the melanin is in the lamina propria, one-third are blue naevi, others are compound naevi, and some are junctional. There is no evidence that most naevi, except rare junctional naevi, progress to melanoma. However, they may resemble melanomas and are best removed to exclude melanoma.

- **Melanoacanthoma:** in some adults of African descent, larger lesions, from 5mm to 2cm in diameter, termed 'melanoacanthomas', may be seen. These are seen mainly in the buccal mucosa or palate in females, may appear rapidly, and are probably reactive lesions. They are best removed.
- **Malignant melanoma:** this is rare but may arise in apparently normal mucosa or in a pre-existent pigmented naevus, usually in the palate or maxillary gingivae. About one-third of melanomas arise in areas of hyperpigmentation. Features suggestive of malignancy include a rapid increase in size, change in colour, ulceration, pain, the occurrence of satellite pigmented spots or regional lymph node enlargement. However, up to 15% of melanomas are amelanotic. Superficial melanomas have a better prognosis than nodular ones. Radical excision is indicated for treatment of melanomas.
- **Kaposi sarcoma** (see Chs 39 and 40).
- **Drugs:** generalized hyperpigmentation or pigmentation may be induced sometimes with pigmentation of skin or other areas:
 - smoking tobacco is now a fairly common cause (smoker's melanosis)
 - antimalarials produce a variety of colours in the mucosa, ranging from yellow with mepacrine to blue-black with amodiaquine
 - zidovudine and ACTH therapy may both produce brown pigmentation
 - busulphan, some other cytotoxic drugs, oral contraceptives, phenothiazines and anticonvulsants may also occasionally produce, or increase, brown pigmentation

- minocycline may cause blackish discolouration of the teeth, gingivae and bone, skin, sclera and even breast milk
- gold may produce purplish gingival discolouration
- many of the other heavy metals formerly implicated in producing oral pigmentation (such as mercury, lead and bismuth) are not used therapeutically now, although industrial exposure still occurs rarely. Metallic sulphides deposited in the tissues were seen especially where oral hygiene was poor, and bacteria produced sulphides, resulting in pigmentation at the gingival margin (e.g. lead line).
- **Addison's disease (hypoadrenalism):** this is uncommon, but may cause generalized or patchy hyperpigmentation due to excessive production of ACTH, which has activities similar to MSH. Addison's disease (adrenocortical hypofunction) is usually autoimmune (idiopathic), but hypoadrenalin may be seen in HIV disease. Hyperpigmentation is generalized, but is most obvious in areas normally pigmented (e.g. the areolae of nipples, genitalia), skin flexures and sites of trauma. The oral mucosa may show patchy hyperpigmentation. Patients with Addison's disease also typically have weakness and weight loss, and hypotension.
- **Nelson syndrome:** this is a rare condition caused by ACTH overproduction in response to adrenalectomy, usually for breast cancer.
- **ACTH-producing tumours:** may induce brown pigmentation, particularly of the soft palate, and may be an oral manifestation of a rare ACTH-producing neoplasm, such as a bronchogenic carcinoma.
- **Peutz-Jeghers syndrome:** in this rare autosomal-dominant condition, oral and circumoral patchy brown pigmentation is seen with small-intestinal polyps.

Diagnosis

The nature of hyperpigmentation can sometimes only be established after further investigation ([Algorithm 12.3](#)).



Algorithm 12.3 Hyperpigmented mucosal lesions

Patients with generalized or multiple hyperpigmentation

- Blood pressure should be taken to exclude Addison's disease (hypotension is characteristic).
- Plasma cortisol levels may be indicated to exclude Addison's disease (low levels found).
- A Synacthen test may be indicated to exclude Addison's disease (impaired response to adrenocorticotrophic hormone found).

Patients with localized hyperpigmentation

- Radiographs may be helpful, as they can sometimes show amalgam, graphite or a foreign body, or bone rarefaction in pigmented neuroectodermal tumour of infancy.
- Photographs may be useful for future comparison of size and colour.
- Urinary catecholamines: in a pigmented neuroectodermal tumour the catecholamines are raised.
- Biopsy may be indicated. If early detection of oral melanomas is to be achieved, all pigmented oral cavity lesions should be viewed with suspicion. The consensus of opinion is that a lesion with the following clinical features is *seriously* suggestive of being a malignant melanoma and is best biopsied at the time of definitive operation:
 - a solitary raised lesion
 - a rapid increase in size
 - change in colour
 - ulceration
 - pain
 - evidence of satellite pigmented spots
 - regional lymph node enlargement.

malignant potential of some (particularly the junctional naevus) and for cosmetic reasons. This is particularly important if the lesions are raised or nodular or have clinical features as above seriously suggestive of being malignant melanoma.

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Management

Management is of the underlying condition. Excision biopsy of isolated hyperpigmented lesions is often recommended to exclude malignancy, because of the

13

Sensory and motor changes and taste abnormalities

Key points

Main causes of orofacial sensory or motor changes

Sensory changes

- Extracranial:
 - trauma (e.g. surgical, fractures)
 - bone disease
 - drugs
 - infections
 - disseminated sclerosis
 - diabetes
 - neoplastic
- Intracranial:
 - trauma (e.g. surgical, fractures)
 - inflammatory
 - neoplastic
 - cerebrovascular disease
 - syringobulbia
 - benign trigeminal neuropathy
 - diabetes
 - bone disease
 - psychogenic
 - drugs
 - disseminated sclerosis

Motor changes (paralysis)

- Upper motor neurone lesion:
 - cerebrovascular accident
 - others
- Lower motor neurone lesion:
 - Bell's palsy (herpes simplex virus usually)
 - tumour affecting facial nerve
 - middle ear disease
 - parotid lesion
 - trauma to facial nerve
 - disseminated sclerosis
 - Guillain-Barré syndrome
 - others

Sensory changes

Normal facial sensation, mediated by the trigeminal nerve, is important to protect the skin, mucosae and especially the cornea from damage. Facial sensory changes, which can be caused by lesions of a sensory branch of

the trigeminal nerve or the central connections (Fig. 13.1), may include sensory awareness that is:

- completely lost (anaesthesia)
- partially lost (hyposensitivity)
- altered (paraesthesia) – often 'pins and needles' or similar discomfort – it may arise during recovery of nerve damage
- increased (hyperaesthesia).

Testing trigeminal function

Trigeminal functions that should be tested include the following:

- Corneal reflex (this tests fifth and seventh cranial nerves); touching the cornea gently with sterile cotton wool should produce a blink.
- Skin sensation, by using:
 - light touch (cotton wool)
 - pin point (sterile needle)
 - temperature
 - vibration
 - two-point discrimination.
- Motor function by palpating:
 - muscles of mastication during function
 - masseters during clenching
 - temporalis during clenching
 - pterygoids during jaw protrusion
 - jaw jerk.

Causes of lesions of a sensory branch of the trigeminal nerve

See Box 13.1.

Extracranial causes

Extracranial causes of facial sensory loss are most common and include damage to the trigeminal nerve from the following causes.

Trauma

This is the usual cause – especially after orthognathic or cancer surgery. If the nerves are stretched or compressed

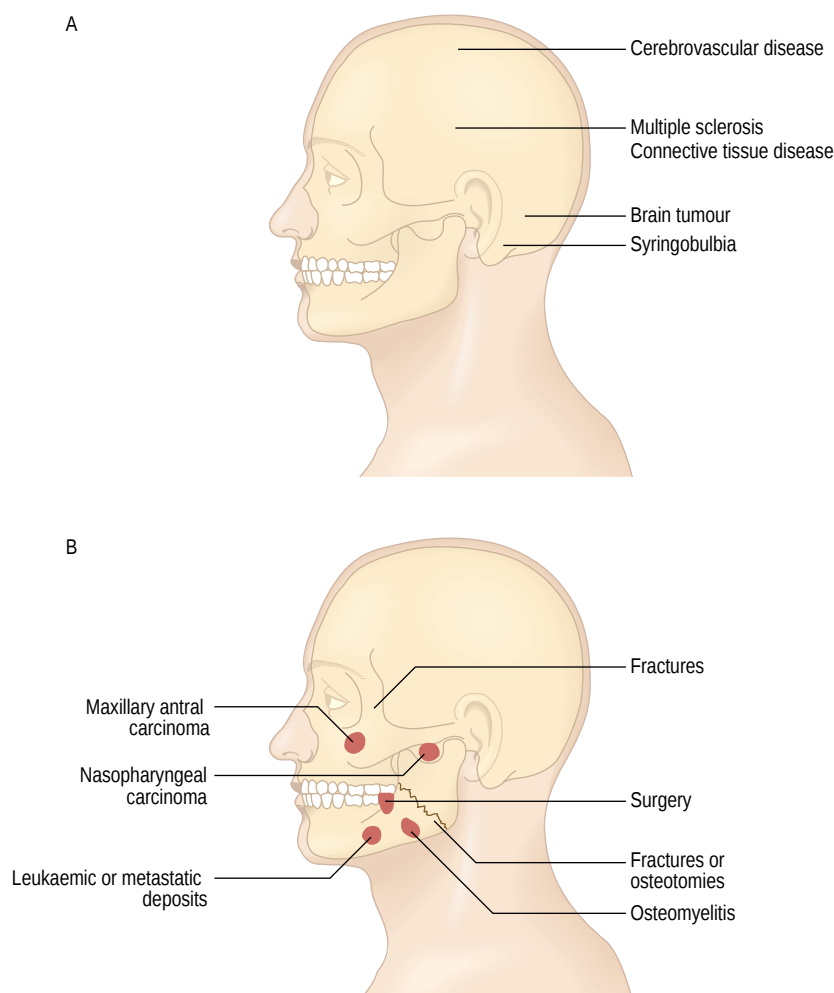


Fig. 13.1 Causes of sensory loss: A, intracranial; B, extracranial

(neuropria), there is often only hypoaesthesia, and recovery of sensation is speedy, typically within days. However, if the nerves are severed (neurotmesis), anaesthesia is profound and recovery is delayed for months accompanied by paraesthesia or hyperaesthesia. Recovery is sometimes not complete:

- Trauma to the mandibular division can have a variety of causes:
 - inferior alveolar local analgesic injections
 - fractures of the mandibular body or angle
 - surgery (particularly surgical extraction of lower third molars, osteotomies or jaw resections) or even endodontics or implants.
- Damage to the mental nerve can have a variety of causes:
 - operations in the region
 - pressure from a denture – the mental foramen is close beneath a lower denture and there is anaesthesia of the lower lip on the affected side.

- The lingual nerve may be damaged, especially during resections or removal of lower third molars, particularly when the lingual split technique is used. Ipsilateral lingual hypoaesthesia or anaesthesia usually result.
- Damage to branches of the maxillary division of the trigeminal nerve may be caused by trauma (usually Le Fort II or III middle-third facial fractures) or surgery.

Bone disease

- Osteomyelitis in the mandible may affect the inferior alveolar nerve to cause labial anaesthesia.
- Paget's disease.

Other causes

- *Drugs* occasionally produce hypoaesthesia (Box 13.1)
- *Disseminated (multiple) sclerosis* may cause sensory loss
- *Diabetes* may produce a neuropathy
- Infections such as syphilis, leprosy or herpesvirus are rare causes.

► Box 13.1

More comprehensive list of causes of facial sensory loss

Extracranial

- Trauma (e.g. surgical, fractures) to inferior dental, lingual, mental or infraorbital nerves
- Inflammatory:
 - osteomyelitis
- Neoplastic:
 - carcinoma of antrum or nasopharynx
 - metastatic tumours
 - leukaemic deposits

Intracranial

- Trauma (e.g. surgical treatment of trigeminal neuralgia)
- Inflammatory:
 - multiple sclerosis
 - sarcoidosis
 - connective tissue disorders
 - infections – neurosyphilis, HIV infection, herpesviruses, tuberculosis, leprosy
- Neoplastic – cerebral tumours
- Vascular:
 - cerebrovascular disease
 - aneurysms
- Syringobulbia
- Drugs:
 - labetalol
 - ritonavir
 - stilbamidine
 - mefloquine
 - methotrexate
 - others
- Bone disease:
 - Paget's disease
 - osteopetrosis

Benign trigeminal neuropathy

- Idiopathic

Psychogenic

- Hysteria
- Hyperventilation syndrome

Endocrine disease

- Diabetes

- Leukaemia, myeloma or metastases (usually from breast, lung, stomach or colon cancer) that may cause deposits in the mandible and labial hypoaesthesia.
- Carcinoma of the maxillary antrum that may produce ipsilateral upper labial hypoaesthesia or anaesthesia.

Intracranial lesions

Intracranial lesions affecting the trigeminal nerve or connections are uncommon but serious. They include:

- *Trauma* including surgical treatment of trigeminal neuralgia
- *Inflammatory disorders*:
 - disseminated sclerosis
 - sarcoidosis
 - infections (e.g. HIV, syphilis)
 - connective tissue disorders.
- *Neoplasms*, such as brain tumours (often metastases).
- *Cerebrovascular disease*:
 - since other cranial nerves are anatomically close, there may be associated neurological deficits in intracranial causes of facial sensory loss
 - in posterior cranial fossa lesions, for example, there may be cerebellar features, such as ataxia
 - in middle cranial fossa lesions there may be associated neurological deficits affecting cranial nerve VI and thus mediolateral eye movements.
- *Syringobulbia*: this leads to sensory loss spreading from the periphery of the face inwards towards the nose, plus a lower motor nerve lesion of the vagus, hypoglossal and accessory nerves, leading to disturbances of speech and swallowing, and bilateral upper motor neurone lesions affecting all limbs. A 'syringomyelia-like' syndrome has been infrequently reported in neurological disorders such as Tangiers disease, lepromatous leprosy and a novel syndrome termed facial onset sensory and motor neuronopathy, or FOSMN syndrome.

Benign trigeminal neuropathy

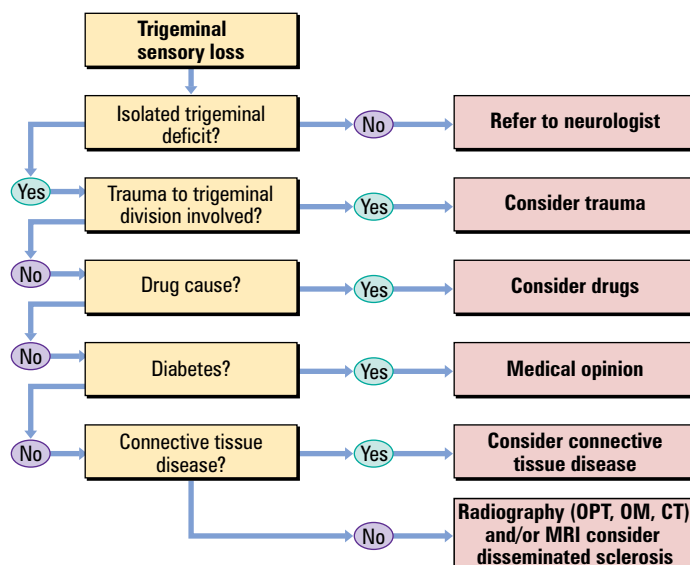
This is a transient sensory loss in one or more divisions of the trigeminal nerve. It seldom occurs until the second decade or affects the corneal reflex. The aetiology is unknown, though some patients prove to have connective tissue disorder.

Psychogenic causes

Hysteria, and particularly hyperventilation syndrome, may underlie some causes of facial anaesthesia/hypoaesthesia. Typically the 'anaesthesia' is bilateral and associated with bizarre neurological complaints.

Neoplastic disease

- Oral carcinomas that may invade the jaws to cause anaesthesia.
- Central malignancies such as osteosarcoma may produce a similar pattern.
- Nasopharyngeal carcinomas that may: invade the pharyngeal wall to infiltrate the mandibular division of the trigeminal nerve, causing pain and sensory loss in the region of the inferior alveolar, lingual and auriculotemporal nerve distributions; invade the levator palati to cause soft palate immobility; and, by occluding the Eustachian tube, cause deafness (Trotter syndrome).



Algorithm 13.1 Sensory loss

Diagnosis

In view of the potential seriousness of facial sensory loss, a full neurological assessment must be undertaken, unless the loss is unequivocally related to local trauma (Algorithm 13.1). Spreading numbness is of particular significance. Possible investigations include:

- imaging (panoral, occipitomental, lateral and postero-anterior skull, and MRI/CT)
- a full blood count, erythrocyte sedimentation rate, random sugar, and syphilis serology.

Management

If there has been neurotmesis, surgical correction can achieve good results. In benign, reversible causes, the underlying cause should be corrected, and the patient reassured that there should be some if not full return of sensation over the subsequent 18 months. Facial hypoaesthesia results in the loss of protective reflexes and a trigeminal trophic syndrome with facial ulceration can follow. If the cornea is anaesthetic or hypoaesthetic, an eye pad should be worn over the closed eyelids, since the protective corneal reflex is lost and the cornea may be damaged.

Taste and abnormalities

What is often called taste is in fact flavour – a combination of taste, smell (aroma), texture (touch sensation) and other physical features (e.g. temperature and spiciness). Smell is a large component of this.

Taste itself drives appetite and protects us from poisons. The special sense of taste is mediated by specialized cells, related to various supporting or sustentacular cells. Taste buds are found in the mucous membrane of the tongue, soft palate, fauces and pharynx, and, in the newborn, on the lips and cheeks. Taste buds on the tongue are on the fungiform, circumvallate and foliate, but not on the filiform, papillae (Fig. 13.2). Papillae at the front of the tongue have more taste buds compared to the mid-region. Taste buds are also located throughout the oral cavity, in the pharynx, the laryngeal epiglottis and at the entrance of the oesophagus. Sensitivity to all tastes is distributed across the whole tongue and to other regions where there are taste buds (epiglottis, soft palate), but some areas are more responsive to certain tastes than others.

Taste buds are oval bodies made up of groups of neuroepithelial and supporting cells. The neuroepithelial cells are rod-shaped with a peripheral hair-like process projecting into the taste pores at the surface of the overlying mucous membrane (Fig. 13.3). The four fundamental varieties of taste sensation do not appear to be detected by structurally different taste buds. The terminal branches of the nerve fibres subserving taste end in close relationship to these special cells. The cells of the taste buds undergo continual renewal, with a life span of about 10 days. Renewal is altered by nutrition, hormonal status, age, drugs, radiation and other factors:

- Fungiform papillae are innervated by the chorda tympani branch of the facial (VIIth cranial) nerve, responding mainly to sodium chloride (NaCl) or to both NaCl and sucrose.
- Foliate papillae are predominantly sensitive to sour tastes. Innervated by the glossopharyngeal (IXth cranial) nerve, responding mainly to bitter.

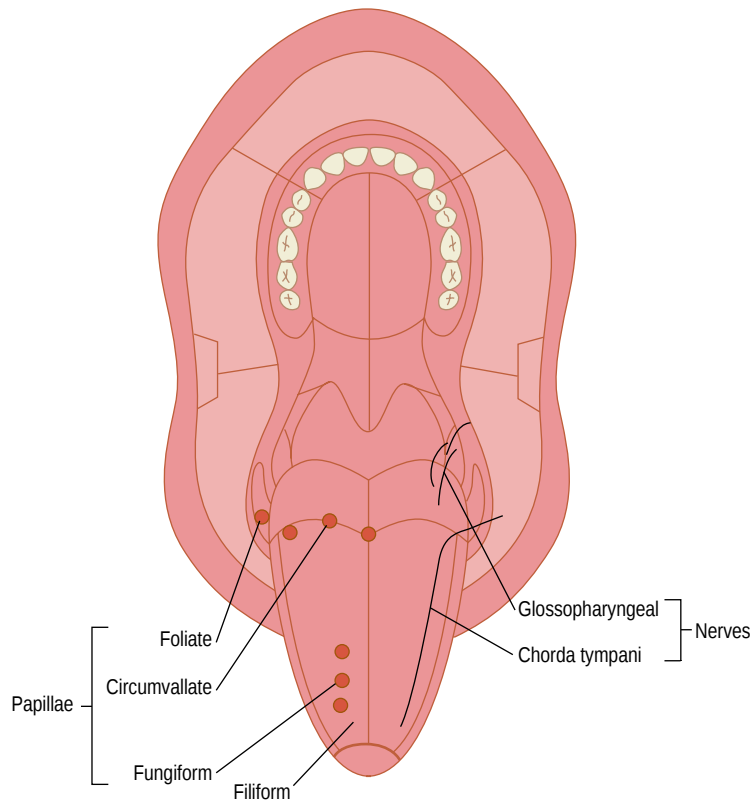


Fig. 13.2 Locations of taste receptors and innervation on tongue

- Circumvallate papillae confer a sour/bitter sensitivity to the posterior two-thirds of the tongue. Innervated by the glossopharyngeal (IXth cranial) nerve, they respond mainly to bitter.

Taste buds transmit information to terminals of sensory nerves which arise from the ganglion cells of branches of cranial nerves VII (the chorda tympani), IX and X:

- Taste sensation from the anterior two-thirds of the tongue and the palate is mediated by the lingual and palatine nerves respectively. The taste fibres pass into the brain stem along the chorda tympani and greater superficial petrosal branches of the facial nerve. The chorda tympani nerve transmits taste impulses, as the nervus intermedius, to the solitary tract, through which the taste impulses are carried to the nucleus solitarius.
- Taste fibres from the posterior third of the tongue pass in the glossopharyngeal nerve to the nucleus solitarius. The taste buds of the epiglottis are innervated by the vagal nerve fibres whose cell bodies are situated in the nodose ganglion and whose central processes terminate once again in the nucleus solitarius.

These primary gustatory fibres synapse in the brain medulla (in the nucleus of the solitary tract) and, from there, the information is relayed to the:

- cerebral somatosensory cortex (for the conscious perception of taste) and
- hypothalamus, amygdala and insula (for the 'affective' component of taste responsible for the behavioural response, e.g. aversion, gastric secretion, feeding behaviour).

There are five basic tastes:

- Salt taste – mediated via sodium chloride (NaCl). Na^+ ions enter the receptor cells via Na^+ channels, cause a depolarization, Ca^{2+} enters through voltage-sensitive Ca^{2+} channels, transmitter release occurs and results in increased firing in the primary afferent nerve.
- Sour taste – mediated by protons (H^+), which block K^+ channels causing depolarization, Ca^{2+} entry, transmitter release and increased firing in the primary afferent nerve.
- Sweet taste – receptors bind glucose, which activates adenylyl cyclase, thereby elevating cAMP, causing phosphorylation of K^+ channels, inhibiting them. Depolarization occurs, Ca^{2+} enters and transmitter is released, increasing firing in the primary afferent nerve.
- Bitter taste – bitter substances cause second messenger (IP_3) mediated release of Ca^{2+} resulting in transmitter release and firing of the primary afferent nerve.
- Umami taste – certain amino acids (e.g. glutamate, aspartate) bind to a metabotropic glutamate receptor (mGluR4)

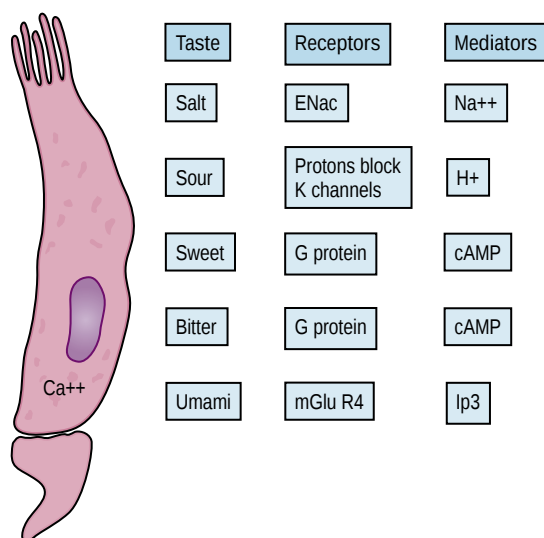


Fig. 13.3 Taste receptor. Ca, calcium; Na, sodium; H, hydrogen; AMP, adenosine monophosphate; K, potassium; Ip3, inositol triphosphate; ENaC, epithelial sodium channels; mGluR4, G protein coupled receptor

activating a G-protein, elevating intracellular Ca^{2+} . Glutamate may also stimulate the ionotropic glutamate receptors (the NMDA-receptor), when non-selective cation channels open, and Ca^{2+} enters, causing transmitter release and increased firing in the primary afferent nerve.

Taste testing

Studies of taste thresholds in human subjects commonly use:

- sucrose for the sweet taste
- vinegar or citric acid to produce sour taste sensations
- sodium chloride for the taste of salt.

Saccharose, quinine solutions, aspartame, acetic acid, citric acid, caffeine, monosodium glutamate (MSG) and inosine 5'-monophosphate (IMP) have also been used. Electrogustometric testing is available using TR-06 (Rion Co. Tokyo, Japan; <http://www.smelltest.com/store/>).

Detection and recognition thresholds can be measured by applying the selected solution to precise regions of the oral mucosa. The tongue, is most sensitive for salt and sweet tastes. Sour and bitter tastes can also be recognized on the tongue, but not as well as by the palatal mucosa. Salt and sweet tastes can be appreciated on the palate also, but higher solution concentrations are required.

Taste changes

Taste and olfaction are both susceptible to the general sensory phenomenon known as adaptation, i.e. the progressive reduction in the appreciation of a stimulus during the

Table 13.1
Terminology of disorders

Dysfunction	Sense of taste
Absence	Ageusia
Diminished	Hypogeusia
Distorted	Dysgeusia
Heightened	Hypergeusia

course of continual exposure to that stimulus. Taste exhibits almost complete adaptation to a stimulus – perception of a substance fades to almost nothing in seconds.

Both taste and olfaction are susceptible to genetic, hormonal, age and other factors:

- For example, sensitivity to the bitter taste of phenylthiourea is genetically determined and some patients are genetically unable, for example, to smell fish. People who have more than the normal number of taste papillae (and taste buds and increased density of fungiform papillae) have extreme sensitivity to n-propylthiouracil (PROP) and are called supertasters. They account for 25% of the population (more women than men) – and tend not to like green vegetables and fatty foods.
- The sense of taste may vary through the menstrual cycle and may be distorted during pregnancy, often with the appearance of cravings for unusual foods.
- The number of taste buds declines with age.
- Taste can be suppressed by local anaesthetics applied to the tongue. Amiloride blocks Na channels and reduces salt taste. Adenosine monophosphate (AMP) may block bitterness. Gymnemic acid (from the Indian tree/shrub *Gymnema sylvestre*) decreases sweet perception. Artichokes, by suppressing sour and bitter taste receptors (the active compounds are chlorogenic acid and cynarin), enhance sweet taste. Miracle fruit via an active ingredient, 'miraculin' makes sour tastes taste sweet.

Taste abnormalities (dysgeusia)

Frequently, when individuals say they cannot taste, the problem is that they cannot appreciate the flavour of food. As the aroma of food contributes to about 75% of its flavour, these individuals usually have suffered a loss of smell ability only.

True taste disorders are uncommon, but may present as a loss of taste, or as an abnormal taste in the mouth, an unpleasant taste, or even an electrical sensation.

Taste impairment ranges from distorted taste to a complete loss of taste – ageusia, hypogeusia (partial taste loss), and dysgeusia (persistent abnormal taste). Some have termed the phantom sensation of bitterness as 'phantogeusia'. The terminologies of the various dysfunctions are shown in Table 13.1.

Taste abnormalities can be caused by anything that interrupts the taste pathways to the brain, or conditions that affect the way the brain interprets taste stimuli (Table 13.2).

Probably the most common causes of loss of senses of taste and smell are viral upper respiratory tract infections, which affect olfaction, but also, thereby, decrease the appreciation of food. Loss of taste is most commonly caused by lingual nerve damage as a result of surgery, tumours, or even dental injections. Abnormal tastes may be caused by injury to the taste buds, injury to the nerves responsible for taste, or to a variety of other conditions. Taste and smell problems have been linked to many medical illnesses, and have been reported as a side-effect to medications, surgery and radiation therapy. Drugs such as antithyroid drugs, captopril, cytotoxic agents, griseofulvin, lithium, penicillamine, procarbazine, rifampin, vinblastine, or vincristine can be responsible.

Disorders of taste sense can be distressing and sometimes incapacitating, and can cause anorexia and depression.

Motor changes

- The facial nerve (seventh cranial) is the motor nerve to the stylohyoid and stapedius muscles and muscles of facial expression, including the:

- orbicularis oculi
- orbicularis oris
- buccinator
- platysma
- scalp and auricle muscles.

- The facial nerve has, besides these motor components:
 - secretomotor fibres – tearing – lacrimal gland
 - saliva production – sublingual, submandibular, nasal and palatine glands
 - nervus intermedius, associated with taste perception in anterior two-thirds of the tongue
 - sensory component.

Facial paralysis

Facial movements may be impaired (palsy), increased or abnormal. In any event, this causes a major cosmetic problem and is very distressing for the patient:

- Facial paralysis (palsy) can be very disfiguring, since the ability to smile is impaired.
- Lesions of the facial nerve central connections (supranuclear or upper motor neurone lesions) or the facial nerve itself (nuclear and infranuclear or lower motor neurone lesions), or muscle disease, can lead to facial weakness.

Table 13.2
Causes of dysgeusia

Mechanism	Main causes	Examples	
		Common	Less common
Olfaction impaired	Nasopharyngeal	Common cold, viral pharyngitis, nasal infection, nasal polyps, sinusitis, influenza	Head injuries, due to tearing of olfactory fibres, and ageing
Receptor local environment changes	Smoking Dry mouth Sepsis	Gastric regurgitation	Sjögren syndrome, salivary gland infections, mouth dryness
Sensory receptor disorders	Ageing (taste bud numbers diminish with age)	Vitamin (B ₁₂) or mineral (zinc) deficiency	Radiation
Cranial nerve disorders	Trauma Neuropathies	Trauma to the mouth, nose, or head, damage to lingual nerve, chorda tympani or facial nerve, e.g. in oral or middle ear surgery.	Bell's palsy Disseminated sclerosis
Cerebral disorders	Trauma Demyelinating disease Cancer Psychogenic disorders	Hypochondriasis Lung cancer	Disseminated sclerosis Parkinson's disease Frontal lobe brain tumours Leukaemia

Causes

Upper motor neurone (UMN) lesions give a palsy that affects mainly the lower parts of the face, since there is bilateral innervation of the upper third of the face. UMN lesions may be due to (Box 13.2 and Fig. 13.4):

- stroke, commonly due to haemorrhage or thrombosis in or around the internal capsule
- a focal lesion which may be moderately selective or cause a cerebral palsy
- a cortical lesion of the cerebral hemispheres, but only rarely.

Lower motor neurone (LMN) lesions give a palsy that affects both the upper and lower parts of the face. Although there is bilateral innervation of the upper third of the face, there is only one common path in the LMN. LMN-related palsy may be due to:

- facial nucleus lesions; such as poliomyelitis, but only rarely
- pontine or posterior cranial fossa lesions. As there are a large number of tracts in close approximation in the pons, the features may be diffuse with frequent bilateral or contralateral involvement. The sixth and eighth cranial nerves are often involved along with the seventh nerve and serve as a good localizing feature in facial palsy. The causes could be:
 - disseminated sclerosis
 - pseudobulbar palsy
 - neoplasm (acoustic neuroma, or even more rarely a meningioma)
 - vascular lesion (basilar artery aneurysm)
 - meningitis
 - intrathecal drug injections (e.g. methotrexate for leukaemia)
 - carcinomatosis.
- Temporal bony canal lesions. The level of involvement can be estimated in three ways: (1) below the geniculate ganglion where lacrimation will be spared; (2) below the chorda tympani where taste from the anterior two-thirds of the tongue is spared; or (3) below the nerve to stapedius which, if involved, may give rise to hyperacusis due to fixation of the stapedius muscle. The causes can be from ganglion peripherally:
 - acute infective polyneuritis (Guillain-Barré syndrome) a peripheral nervous system affliction often following a viral infection and manifesting mainly with weakness or tingling sensations in the legs. In many instances, the weakness and abnormal sensations spread to the arms and upper body.

► Box 13.2

Main causes of facial palsy (paralysis)

Upper motor neurone lesion

- Cerebrovascular accident
- Trauma
- Tumour
- Infection
- Multiple sclerosis
- Moebius syndrome
- Connective tissue disease

Lower motor neurone lesion

- Systemic infection
 - Bell's palsy (herpes simplex virus usually)
 - HIV infection
 - HTLV-1 infection
 - Lyme disease (*Borrelia burgdorferi*)
 - Varicella-zoster virus infection (± Ramsay-Hunt syndrome)
 - Cytomegalovirus, Epstein-Barr virus and influenza viruses

Other

- Other infections, e.g. leprosy, Guillain-Barré, Kawasaki disease
- Diabetes
- Middle-ear disease:
 - otitis media
 - cholesteatoma
- Lesion of skull base:
 - fracture
 - infection
 - sarcoidosis
- Parotid lesion:
 - tumour
- Trauma to branch of facial nerve
- Inferior dental regional anaesthetic affecting the facial nerve
- Barotrauma
- Melkersson-Rosenthal syndrome/Crohn's disease

- Ramsay-Hunt syndrome, caused by varicella-zoster virus infection, which allegedly involves the facial nerve at the geniculate ganglion
- fracture of the temporal bones of the skull can involve the nerve anywhere in the bony canal in that bone
- haemorrhage may occur into the canal in hypertensive states
- leukaemic and other malignant deposits or sarcoid are rare causes
- middle-ear conditions, which may be the cause and include:
 - chronic otitis media
 - cholesteatoma
 - ear surgery, especially mastoidectomy.
 - Bell's palsy can involve the nerve anywhere in the bony stylomastoid canal

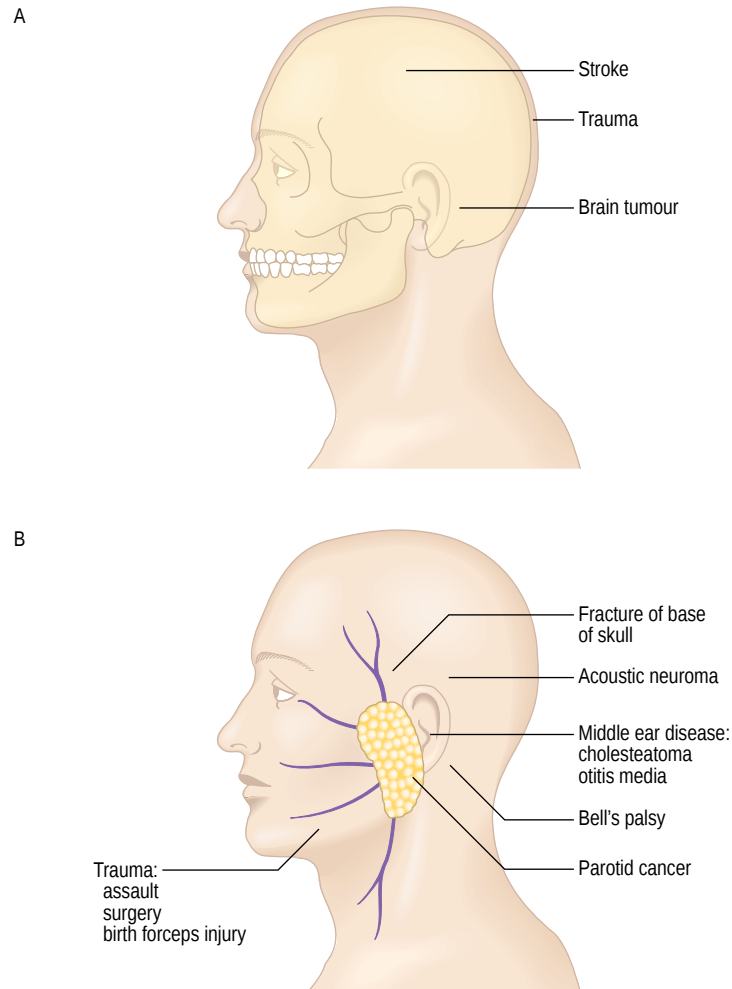


Fig. 13.4 Causes of facial palsy: A, upper motor neurone lesions; B, lower motor neurone lesions of the seventh nerve

- damage caused to the nerve after leaving the stylo-mastoid canal.
- trauma: barotrauma or use of forceps in delivery, stab wounds and facial lacerations can cause facial paralysis
- parotid lesions: benign tumours in the main displace the facial nerve, but malignant tumours infiltrate the nerve and cause paralysis.
- sarcoidosis of the parotid gland (as part of uveoparotitis) and Crohn's and related conditions are rare causes
- leprosy. It may be possible to palpate the nerve as a cord which can be rolled under the skin.
- Lesions involving the facial nerve (e.g. assault with a knife or bottle, malignant tumours in, or surgery to, the parotid or submandibular region).
- Occasionally, a temporary facial palsy follows the (mal-)administration of an inferior alveolar local analgesic, if the anaesthetic diffuses from the pterygomandibular space distally through the parotid gland, when it can reach and temporarily paralyze the facial nerve.

However, the common causes of facial paralysis are:

- Strokes, seen mainly in older males and usually caused by a cerebrovascular accident.
- Bell's palsy, seen mainly in younger patients and thought for many years to be idiopathic. However, it is mainly related to infection and swelling within the confines of the stylomastoid canal, usually due to herpes simplex virus.

Patterns of facial weakness

Laterality and level are important clinical features.

- Upper motor neurone lesions (supranuclear lesions) will produce lower facial weakness. The weakness does not affect the forehead, which has bilateral cortical representation. The neurological lesion is contralateral to the lower facial weakness. The causes include vascular events such as strokes, tumours and demyelination.

- Lower motor neurone lesions (infranuclear lesions) produce full ipsilateral hemifacial weakness, including the forehead.

Differentiating nuclear from infranuclear lesions depends on the presence of other neurological signs. Contralateral limb weakness suggests a pontine level lesion and therefore a nuclear facial nerve lesion. Cerebello-pontine angle lesions typically affect multiple cranial nerves as well as producing hyperacusis and disturbances of lacrimation, taste and salivation. Lacrimation is affected in a proximal lesion of the facial canal, but is spared in a more distal lesion. Salivation and taste are affected by all facial canal lesions. Facial level lesions affect only muscle function, leaving lacrimation, salivation and taste intact.

Clinical features

In facial palsy, the patient typically complains of impaired:

- smile
- speech
- ability to whistle.

In addition, on the affected side:

- the forehead is unfurrowed
- the patient is unable to close the eye
- the eye rolls upward (Bell's sign) on attempted closure
- tears tend to overflow onto the cheek (epiphora)
- the nasolabial fold is obliterated
- the corner of the mouth droops
- saliva may dribble from the commissure
- food collects in the vestibule
- plaque accumulates on the teeth.

Depending on the site of the lesion, other features such as loss of taste may be associated.

Upper motor neurone palsy

The neurones to the upper face receive bilateral UMN innervation. UMN facial palsy is usually caused by damage in the middle capsule of the brain. Damage thus extends to include hemiplegia and sometimes affects speech, but extrapyramidal influences remain and thus there can still be involuntary facial movements, for example, on laughing because of the bilateral cortical representation. A UMN lesion, therefore, is characterized by:

- contralateral facial palsy
- some sparing of the frontalis and orbicularis oculi muscles
- spontaneous facial movements with emotional responses.

There may also be aphasia and on the side of facial palsy:

- paresis of the arm (monoparesis)
- paresis of the arm and leg (hemiparesis).

Lower motor neurone palsy

In contrast, LMN facial palsy is characterized by:

- total unilateral paralysis of all muscles of facial expression
- absence of voluntary and emotional facial responses
- no hemiparesis or aphasia.

Diagnosis

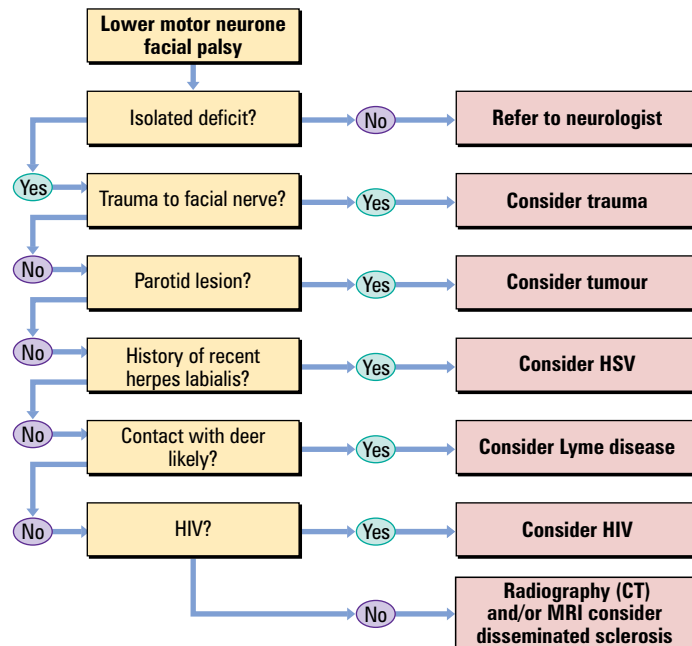
The history should be directed to elicit features suggestive of stroke, trauma, including underwater diving (barotrauma), camping or walking in areas that may contain ticks (Lyme disease), the possibility of HIV infection and, in Afro-Caribbeans, the possibility of HTLV-1 infection. A facial paresis which is slowly evolving, associated with other focal neurology, facial twitching, multiple cranial nerve deficits or with chronic Eustachian tube dysfunction suggests a possible malignant cause. A neck or parotid mass or history of previous head or neck malignancy is suspicious ([Algorithm 13.2](#)).

The examination should include the following:

- Ear and mouth examination to exclude Ramsay-Hunt syndrome (herpes zoster of the facial nerve ganglion which causes lesions in the palate and ipsilateral ear, and facial palsy).
- Ear examination to look for discharge and other signs of middle-ear disease.
- A full neurological examination, especially to exclude lesions of other cranial nerves, and to exclude a stroke. The facial nerve weakness is demonstrated by asking the patient to:
 - close the eyes against resistance
 - raise the eyebrows
 - raise the lips to show the teeth
 - try to whistle.
- A test for loss of hearing should be carried out.
- A test for taste loss should be carried out.

Investigations that may be indicated include the following:

- A study of evoked potentials to assess the degree of nerve damage. Facial nerve stimulation or needle electromyography may be useful, as may electrogustometry.
- Imaging with CT/MRI, and chest and skull radiography to look particularly for central lesions.



Algorithm 13.2 LMN facial palsy

- Blood pressure measurement should be carried out to exclude hypertension.
- Fasting blood sugar levels should be tested to exclude diabetes.
- In some areas, Lyme disease (tick-borne infection with *Borrelia burgdorferi*) should be excluded by enzyme-linked immunosorbent assay (ELISA).
- Tests for virus infections, such as HSV, VZV, HIV or HTLV-1, may need to be considered.
- Serum angiotensin converting enzyme (ACE) levels to exclude sarcoidosis.
- Lumbar puncture is needed occasionally.

Management

Management is of the underlying condition. Most patients with Bell's palsy are otherwise healthy and present no other management difficulties, but there are occasional (possibly coincidental) associations with diabetes mellitus, hypertension and lymphoma.

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14 Soreness and ulcers

Key points

Main causes of mouth ulcers

- **Systemic disease:**
 - blood disorders
 - infections
 - gastrointestinal disease
 - skin diseases
- **Malignant neoplasms**
- **Local causes**
- **Aphthae**
- **Drugs**

'So many laws and directives'
'bigs'

Introduction

The mouth can be sore for a number of reasons, especially where there are distinct conditions, such as:

- Dry mouth – which predisposes to soreness, since the lubricating and protective functions of saliva are reduced and infections, such as candidiasis, are more common.
- Epithelial thinning or breaches can also result in soreness. This occurs in:
 - mucosal inflammation: any inflammatory lesion can cause soreness; candidiasis is one example (antibiotic sore tongue)
 - mucosal atrophy: this is the term often used for thinning of the epithelium, which has a red appearance since the underlying lamina propria shows through. Most commonly seen in geographic tongue (erythema migrans, benign migratory glossitis), atrophy may also be seen in lichen planus or systemic disorders, such as deficiency states (of iron, folic acid or B vitamins)
 - mucosal erosions: this is the term used for superficial breaches of the epithelium, which often initially have a red appearance, since there is little damage to the underlying lamina propria. If a breach penetrates the full thickness of the epithelium, however, it typically becomes covered by a fibrinous exudate and then has a yellowish appearance. Erosions are common in radiation-induced mucositis and in lichen planus

- mucosal ulcers: this is the term used usually where there is damage to both epithelium and lamina propria, and then a crater forms, sometimes made more obvious clinically by oedema or proliferation causing swelling of the surrounding tissue (Fig. 14.1). An inflammatory halo, if present, also highlights the ulcer with a red halo, around the yellow or grey ulcer. Ulcers are common in recurrent aphthous stomatitis. Most other ulcers/erosions are due to local causes, such as trauma or burns, but neoplasms and systemic disorders must always be considered
- Dry mouth and epithelial thinning can result from irradiation of the oral region.

Soreness may also be encountered in an apparently normal mouth with no clinical signs of any of the above. This can be due to:

- subclinical disease, such as a deficiency state, particularly of vitamin B₁₂, or even anaemia
- psychogenic causes, which can underlie a sore tongue or sore mouth (often described as a burning sensation) – sometimes known as oral dysaesthesia
- neuropathies, such as in diabetes mellitus.

Ulcers

- Ulcers and erosions can be the final common manifestation of a spectrum of conditions ranging from epithelial damage resulting from an immunological attack – as



Fig. 14.1 Ulceration in acute necrotizing gingivitis destroys the interdental papillae particularly

in pemphigus, pemphigoid or lichen planus – to damage because of an immune defect as in HIV disease and leukaemia, infections as in herpesviruses, tuberculosis and syphilis, or nutritional defects, such as in vitamin deficiencies and some intestinal disease (Box 14.1).

- The most important feature of ulceration is whether the ulcer is persistent, since this may indicate that the ulcer is caused by a chronic condition:
 - neoplasia, such as carcinoma
 - trauma
- skin disease, such as pemphigus
- infection, such as syphilis, tuberculosis or a mycosis.
- An important feature is whether one or more than one ulcer is present, since malignant tumours usually cause a single lesion. A single ulcer persisting for more than 3 weeks without signs of obvious healing must be taken seriously, as it could be a neoplasm or chronic infection.
- Multiple persistent ulcers are mainly caused by:
 - blood diseases, such as leukaemia

► Box 14.1

Main causes of mouth ulcers

Systemic disease

- Blood disorders:
 - anaemia
 - gammopathies
 - haematinic deficiencies
 - hypereosinophilic syndrome
 - leukaemias
 - myelodysplastic syndromes
 - neutropenia
 - other white cell dyscrasias
- Infections:
 - viruses:
 - chickenpox
 - hand, foot and mouth disease
 - herpangina
 - herpetic stomatitis
 - HIV
 - infectious mononucleosis
 - bacteria:
 - acute necrotizing gingivitis
 - syphilis
 - tuberculosis
 - fungi:
 - blastomycosis
 - cryptococcosis
 - histoplasmosis
 - paracoccidioidomycosis
 - parasites:
 - leishmaniasis
- Gastrointestinal disease:
 - coeliac disease
 - Crohn's disease (and orofacial granulomatosis)
 - ulcerative colitis
- Skin disease:
 - chronic ulcerative stomatitis
 - dermatitis herpetiformis
 - epidermolysis bullosa
 - erythema multiforme
 - lichen planus
 - linear IgA disease
 - pemphigoid and variants
 - pemphigus vulgaris
 - other dermatoses

- Others:
 - rheumatic diseases:
 - lupus erythematosus
 - Sweet syndrome
 - Reiter syndrome
 - Vasculitides:
 - Behçet syndrome
 - Wegener's granulomatosis
 - periarthritis nodosa
 - giant cell arteritis
 - Endocrine disorders:
 - diabetes
 - glucagonoma
 - Disorders of uncertain pathogenesis:
 - eosinophilic ulcer
 - necrotizing sialometaplasia

Malignant neoplasms

Oral or encroaching from antrum, salivary glands, nose or skin:

- Carcinomas
- Lymphomas
- Sarcomas
- Others

Local causes

- Trauma:
 - sharp teeth or restorations
 - appliances
 - non-accidental injury
 - self-inflicted
 - iatrogenic
- Burns:
 - heat
 - cold
 - chemical
 - radiation
 - electric

Aphthae

(Recurrent aphthous stomatitis) and PFAPA (see Ch.39)

Drugs

- Alendronate
- Cytotoxics
- NSAIDs
- Nicorandil
- Propylthiouracil
- Many others

- infection or immune defect
- gastrointestinal disease
- skin diseases, such as pemphigus, pemphigoid or lichen planus
- Multiple non-persistent ulcers can be caused by aphthae, when the ulcers heal spontaneously, usually within 1 week to 1 month. If this is not the case, an alternative diagnosis should be considered.
- Erosions or ulcers on both sides at the commissures of the lips are usually angular stomatitis (cheilitis), but sores are also sometimes caused at the angles by trauma (such as dental treatment) or infection (such as recurrent herpes labialis).
- A useful mnemonic to remember the main causes is 'So many laws and directives' (systemic; malignant; local; aphthae; drugs), and the systemic causes are mainly blood; infections; gastrointestinal and skin diseases ('bigs').

Systemic disease

A wide range of systemic diseases, especially blood, infectious, gut and skin disorders ('bigs'), may cause oral lesions, which, because of the moisture, trauma and infection in the mouth, tend to break down to leave ulcers or erosions (Box 14.1).

- Blood (haematological) disease can cause ulcers. Mouth ulcers may be seen in leukaemias and myelodysplastic syndromes, associated with cytotoxic therapy, with viral, bacterial or fungal infection, or be non-specific. Other oral features may include purpura, gingival bleeding, lymphadenopathy, recurrent herpes labialis and candidiasis. Hypereosinophilic syndrome may present with ulcers.
- Infective causes of mouth ulcers include mainly viral infections, especially the herpesviruses. Other viruses that may cause mouth ulcers include Coxsackie, echo and HIV viruses. Bacterial causes of mouth ulcers are less common, apart from acute necrotizing (ulcerative) gingivitis. Syphilis, either the primary or secondary stages, and tuberculosis have been uncommon in the developed world, but are increasing, especially in HIV/AIDS. Fungal causes of ulcers are also uncommon in the developed world, but are increasingly seen in immunocompromised persons and travellers. Protozoal causes of ulcers, such as leishmaniasis, are rare in the developed world, but are appearing in HIV/AIDS. Other causes are shown in Table 14.1.
- Gastrointestinal disorders may result in soreness or mouth ulcers. Some patients with aphthae have intestinal disease, such as coeliac disease, causing malabsorption and deficiencies of haematinics, when they may also develop angular stomatitis or glossitis. Crohn's disease and pyostomatitis vegetans may cause ulcers. Orofacial granulomatosis (OFG), which

has many features reminiscent of Crohn's disease, may also cause ulceration.

- Skin (mucocutaneous) disorders that may cause oral erosions or ulceration (or occasionally blisters) include particularly lichen planus, occasionally pemphigoid, and rarely pemphigus, erythema multiforme and epidermolysis bullosa.
- Other causes include the following:
 - Rheumatic diseases – lupus erythematosus, rheumatoid disease and Reiter syndrome.
 - Vasculitides – Behçet syndrome, periarteritis nodosa, Wegener's granulomatosis and giant cell arteritis.
 - Endocrine causes – diabetes or glucagonoma.
 - Disorders whose pathogenesis is uncertain – eosinophilic ulcer, necrotizing sialometaplasia (see Ch. 39), sarcoidosis, periodic fever, aphthae, pharyngitis and adenitis (PFAPA) (see Ch. 39).

Malignant ulcers

A range of neoplasms may present with ulcers, most commonly these are carcinomas, but Kaposi sarcoma, lymphomas and other neoplasms may be seen (see Ch. 20).

Local causes

- At any age there may be factitious ulceration, especially of the maxillary gingivae, or burns with chemicals of various kinds, heat, cold, or ionizing radiation.
- In children they are usually caused by accidental biting, or following dental treatment or other trauma, hard foods or appliance. In child abuse (non-accidental injury), ulceration of the upper labial fraenum may follow a traumatic fraenal tear. Bruised and swollen lips, and even subluxed teeth or fractured mandible, can be other features of child abuse. The lingual fraenum may be traumatized by repeated rubbing over the lower incisor teeth in children with recurrent bouts of coughing as in whooping cough (termed Riga-Fedes disease) or in self-mutilating conditions. Chronic trauma may produce an ulcer with a keratotic margin.
- Trauma can produce ulceration in adults. Sometimes the lingual fraenum is damaged by trauma in cunnilingus, or the palate in fellatio.

Aphthae (recurrent aphthous stomatitis; RAS)

Ulcers are commonly aphthae, usually in persons who are otherwise well. Occasionally they are associated with haematinic deficiencies, or are part of Behçet syndrome (see Ch. 19) or PFAPA (see Ch. 39).

Table 14.1
Infectious diseases that may produce oral ulceration

Disease	Causal agent	Major manifestations
AIDS (HIV infection)	HIV	Pneumonia, Kaposi sarcoma, lymphomas, general lymphadenopathy, candidiasis, herpes simplex virus, hairy leukoplakia, periodontal disease, ulcers, cervical lymph node enlargement
Chickenpox (varicella)*	VZV	Rash evolves through macule, papule, vesicle and pustule; rash crops and is most dense on trunk. General lymphadenopathy, oral ulcers, cervical lymph node enlargement
Cytomegalovirus*	CMV	Glandular-fever-type syndrome (Paul-Bunell negative), general lymphadenopathy
Gonorrhoea	<i>Neisseria gonorrhoea</i>	Urethritis, pharyngitis
Hand, foot and mouth disease	Coxsackie viruses	Rash, minor malaise, oral ulceration (usually mild)
Herpangina	Coxsackie viruses	Fever, sore throat, vesicles and ulcers on soft palate, cervical lymph node enlargement
Herpes simplex*	HSV	Fever, oral ulceration, gingivitis, gingivostomatitis, herpes labialis (secondary infection), cervical lymph node enlargement
Herpes zoster* (shingles)	VZV	Rash like chickenpox, but limited to dermatome. Severe pain. Oral ulceration in zoster of maxillary or mandibular division of trigeminal nerve. Ulcers on palate and in pinna of ear in Ramsay-Hunt syndrome
Infectious mononucleosis	EBV	Fever, pharyngitis, general lymphadenopathy, tonsillar exudate, palatal petechiae, oral ulceration
Mucocutaneous lymph node syndrome (Kawasaki disease)	?	Rash, hands and feet desquamation, general lymphadenopathy, myocarditis, strawberry tongue, labial oedema, pharyngitis
Mycoplasma pneumonia (atypical pneumonia)	Mycoplasma	Sore throat, fever, pneumonia, erythema multiforme occasionally
Pertussis† (whooping cough)	<i>Bordetella pertussis</i>	Cough, fever, occasionally ulceration of lingual fraenum
Syphilis	<i>Treponema pallidum</i>	Chancre, lymphadenopathy, rash, ulceration, mucous patches
Toxoplasmosis*	<i>Toxoplasma gondii</i>	Glandular-fever-type syndrome (Paul-Bunell negative), general lymphadenopathy, cough, sore throat
Tuberculosis*	<i>Mycobacterium tuberculosis</i>	Ulceration, fever, weight loss, general lymphadenopathy

*Prevalent and often widespread infections in the immunocompromised, high-risk patients such as organ transplant, HIV or leukaemic patients.

†Some cases are caused by *Bordetella parapertussis* or by viruses.

Drug-induced ulceration

Drugs may induce ulcers by producing a local burn or by a variety of mechanisms. Cytotoxic drugs (e.g. methotrexate), non-steroidal anti-inflammatory drugs (NSAIDs), alendronate and nicorandil (a potassium channel activator used in cardiac disorders) may be the cause.

Diagnosis

Making a diagnosis of the cause for oral soreness or ulceration is based mainly on the history and clinical features. The number, persistence, shape, character of the edge of the ulcer and the appearance of the ulcer base should also be noted. Ulcers should always be examined for induration (firmness on palpation), which may be indicative of malignancy. Unless the cause is undoubtedly local, general physical examination is also indicated, looking especially for mucocutaneous lesions, lymphadenopathy or fever ([Algorithms 14.1–14.6](#)).

Features that might suggest a systemic background to mouth ulcers include:

- extraoral features such as:
 - skin lesions
 - ocular lesions
 - anogenital lesions
 - purpura
 - fever
 - lymphadenopathy
 - hepatomegaly
 - splenomegaly
 - chronic cough
 - gastrointestinal complaints (e.g. pain, altered bowel habits, blood in faeces)
 - loss of weight or, in children, a failure to thrive
 - weakness
- an atypical history or ulcer behaviour such as:
 - onset of ulcers in later adult life
 - exacerbation of ulcers
 - severe aphthae
 - aphthae unresponsive to topical hydrocortisone or triamcinolone
- other oral lesions, especially:
 - candidiasis
 - herpetic lesions
 - glossitis
 - petechiae
 - gingival bleeding
 - gingival swelling
 - necrotizing gingivitis or periodontitis
 - hairy leukoplakia
 - Kaposi sarcoma.

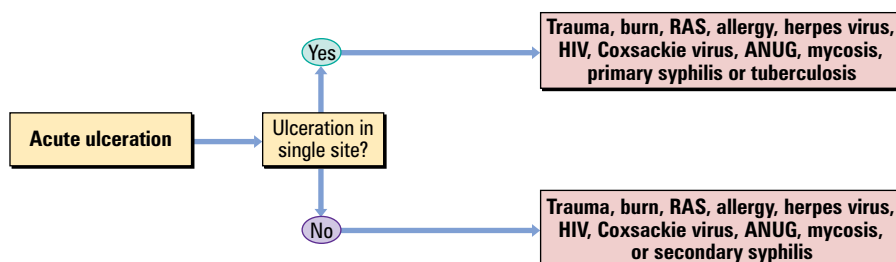
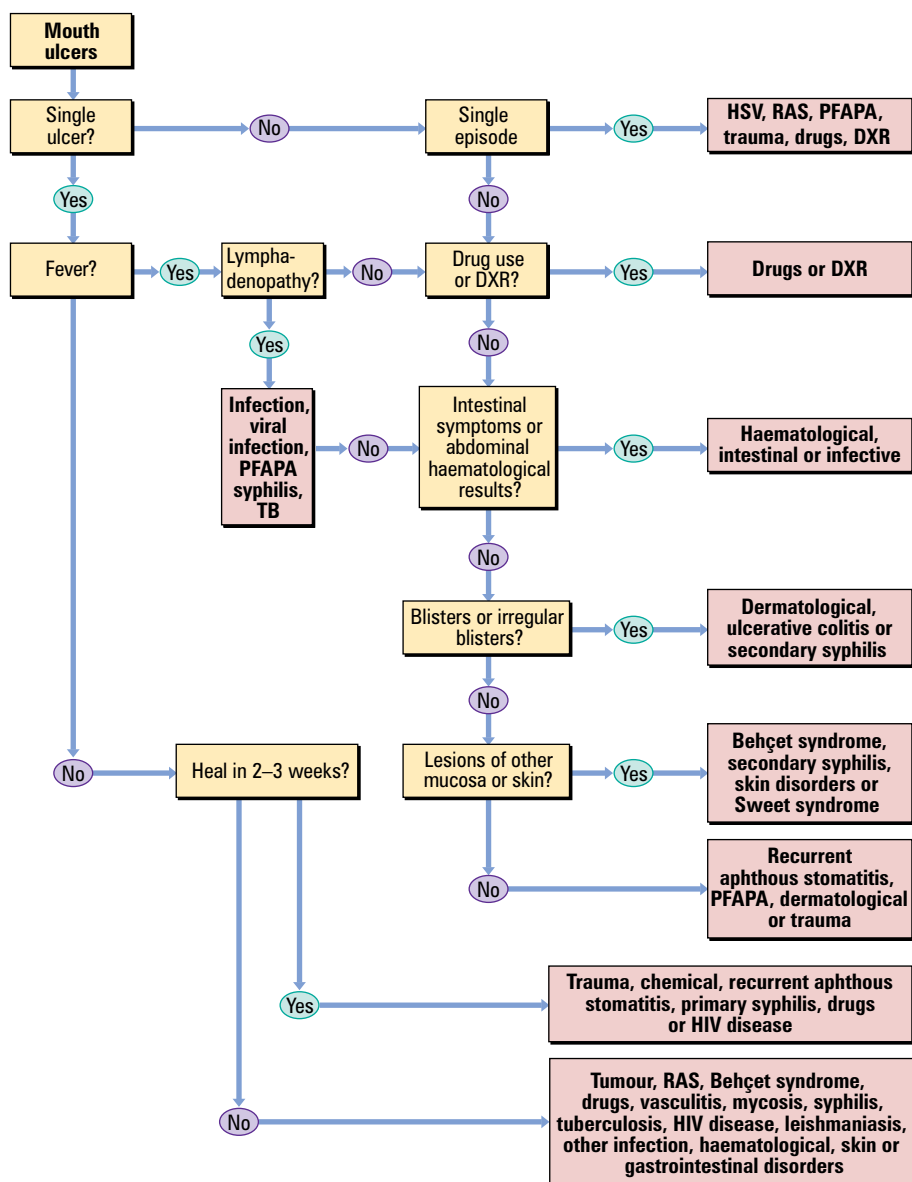
Investigations

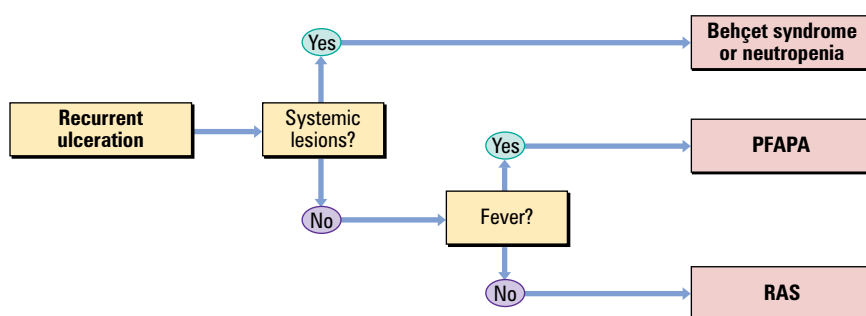
Investigations that may sometimes be indicated include the following:

- Blood tests – may be useful for excluding possible deficiencies or other conditions when a systemic cause, such as leukaemia, EBV or HIV infection, is suspected.
- Microbiological and serological investigations – may be needed, especially if microbial causes are suspected.
- Glucose assays (urine and blood) – may occasionally be needed to exclude diabetes.
- Biopsy – may be needed, especially where there:
 - is a single ulcer persisting for more than 3 weeks
 - is an ulcer that might have been traumatic in aetiology, but persists for more than 3 weeks after relief from the trauma
 - is induration
 - are skin lesions
 - are lesions in other mucosae
 - are other related systemic lesions, signs or symptoms.
- Imaging and other special investigations – may be indicated where there are possible lesions, such as tuberculosis, the deep mycoses, carcinoma or sarcomatosis.

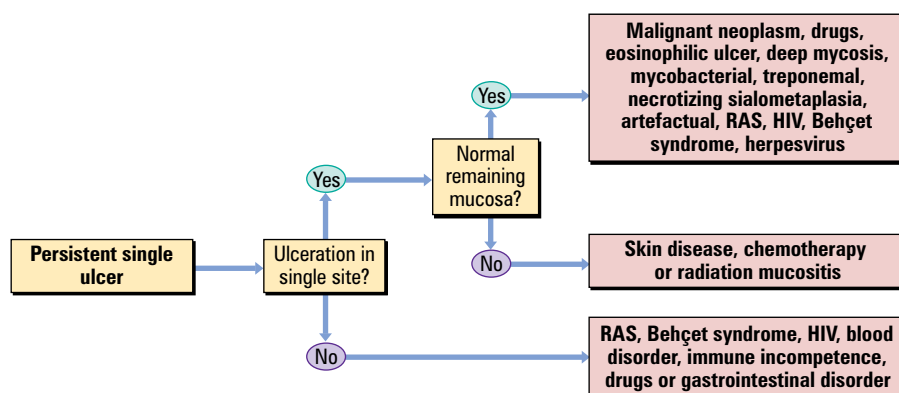
Management (Fig. 14.2)

- Treat the underlying cause.
- Remove aetiological factors.
- Ensure any possible traumatic element is removed (e.g. a denture flange).
- Prescribe a chlorhexidine 0.2% aqueous mouthwash.
- Maintain good oral hygiene.
- A benzydamine mouthwash or spray, or silver nitrate application to an ulcer may help ease discomfort.
- Topical corticosteroids are useful in the management of many oral ulcerative conditions where there is no systemic involvement, such as recurrent aphthous stomatitis and oral lichen planus (see [Box 14.1](#)).
- Steroid creams, gels and inhalers are better than ointments since the latter adhere poorly to the mucosa. However, creams can be bitter and gels can irritate.
- Patients should not eat or drink for 30 minutes after using the steroid, in order to prolong contact with the lesion.
- Adverse effects are important mainly with systemic steroids. With many topical steroids there is little systemic absorption and thus no significant adrenocortical suppression. In patients using potent topical steroids for more than a month it is prudent to add an antifungal, since candidiasis may arise.

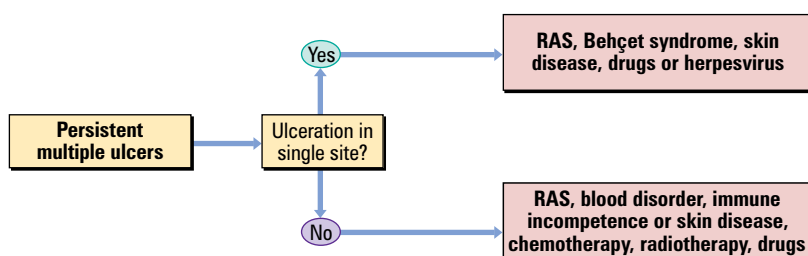




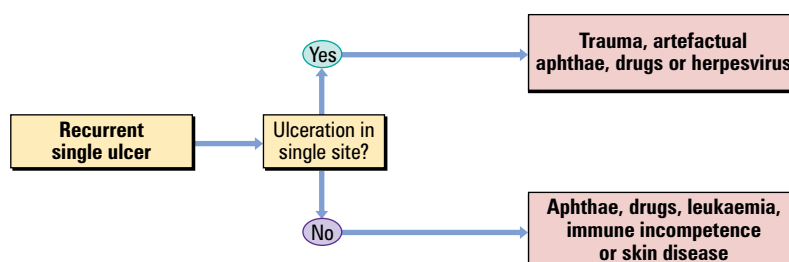
Algorithm 14.3 Recurrent ulcers



Algorithm 14.4 Persistent single ulcers



Algorithm 14.5 Persistent multiple ulcers



Algorithm 14.6 Recurrent single ulcers

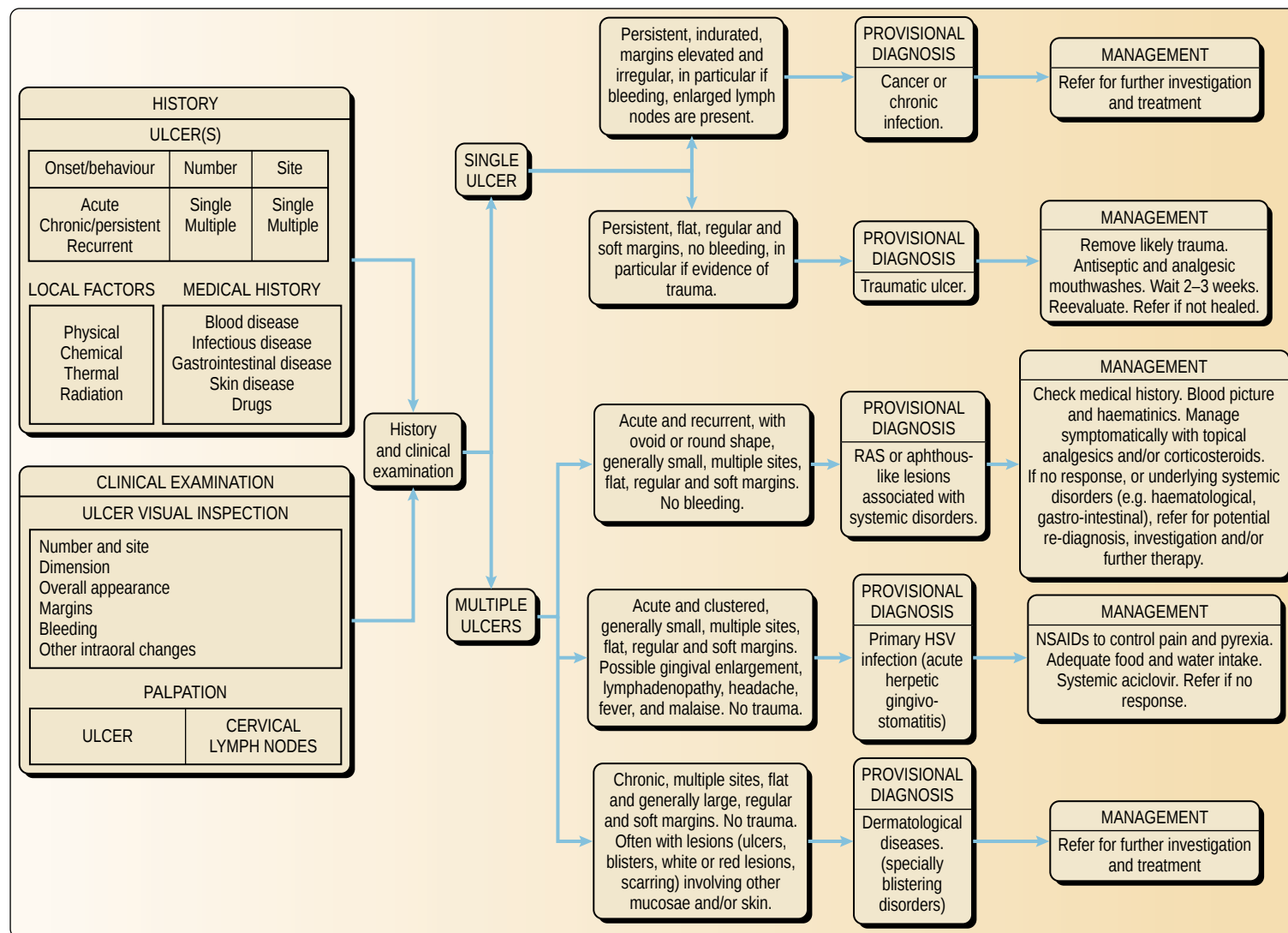


Fig. 14.2 Overall flow diagram for ulcer management. Courtesy of Scully, Fedele and Porter, BMJ 2007 (in press)

Other topical immunomodulatory agents

Topical immunosuppressants, such as tacrolimus, can be:

- effective in ulcerative disorders
- more effective if used along with topical corticosteroids
- expensive
- associated with adverse effects only rarely.

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SECTION 3

COMMON AND IMPORTANT ORAL CONDITIONS

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15

Angioedema (angioneurotic oedema)

Key points

- Angioedema is acute oral or facial swelling
- Oedema may hazard the airway
- Most cases are allergic
- Intramuscular adrenaline (epinephrine) may be indicated.

Introduction

The lips can swell in either allergic angioedema (a type 1 hypersensitivity response seen mainly in those with an atopic tendency) (Fig. 15.1) or hereditary angioneurotic oedema (HANE; caused by a deficiency of the complement component C1 esterase inhibitor – C1-INH). Rarely there is an acquired C1-INH deficiency.

Angioedema manifests with oral or facial swelling of acute onset with rapid development of oedematous swelling of the lip(s) and tongue. The danger is that oedema may also involve the neck and hazard the airway. The swelling in angioedema is usually relatively transient and the skin does not scale.

Allergic angioedema

Incidence

It is common – far more common than HANE.



Fig. 15.1 Lip swelling in angioedema

Age

It occurs mainly in adults.

Sex

It is most prevalent in females.

Geographic

No known geographic incidence.

Aetiology

Allergic angioedema is a type 1 reaction that may be induced by:

- foods: nuts are a well-known cause
- drugs:
 - antibiotics
 - aspirin
 - others
- other allergens.

Clinical features

- The oedema can cause pronounced labial and periorbital swelling, and can involve any oral site, but when oedema involves the tongue and neck and extends to the larynx, it can cause rapidly fatal respiratory obstruction.
- Acute allergic oedema of this type can develop alone or may be associated with anaphylactic reactions (and/or urticaria).

Diagnosis

Angioedema is diagnosed clinically and from a history of atopic disease and/or exposure to allergen, and sometimes by allergy testing (prick test), but an emergency kit must always be at hand.

Management

Although the swelling is of acute onset and often only mild and transient, there is always the potential of obstruction of the airway, and thus urgent treatment is indicated.

- In severe cases, especially if there is any potential or real threat to the airway, the emergency should be managed with intramuscular adrenaline (epinephrine), and with systemic corticosteroids or antihistamines – as for an anaphylactic reaction.
- Mild angioedema may respond to antihistamines, such as chlorpheniramine, or to a sympathomimetic agent, such as ephedrine by mouth.
- For rare intractable chronic cases, corticosteroids may be required.

Drug-induced non-allergic angioedema

Non-allergic oral swelling can arise in response to angiotensin converting enzyme (ACE) inhibitor therapy due to a rise in levels of bradykinins and/or altered levels or function of C1 esterase inhibitor. The swelling usually affects the lips, although it can be localized to the tongue, and is occasionally fatal. People of African heritage may be at particular risk of this adverse drug reaction.

Hereditary angioedema (HANE: C1 esterase inhibitor deficiency)

HANE mimics allergic angioedema, though it produces a more severe reaction. Despite its hereditary nature, usually as an autosomal dominant trait, the disease may not present until later childhood or adolescence, and nearly 20% of cases are caused by spontaneous mutation.

Incidence

It is uncommon.

Age

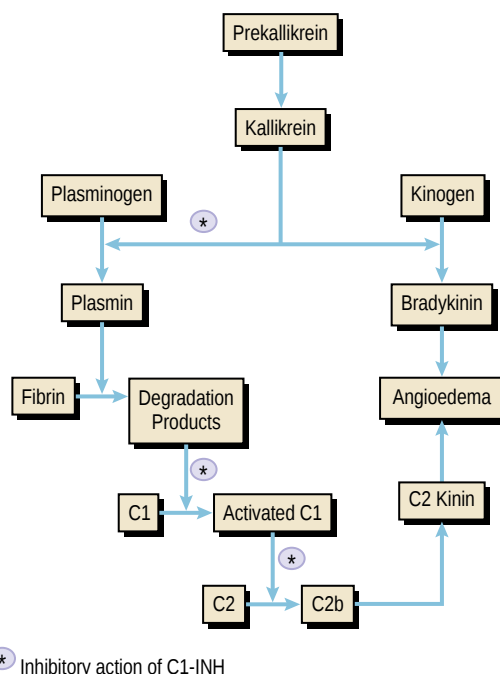
It can occur at any age.

Sex

It occurs equally in both sexes.

Geographic

No known geographic incidence.



* Inhibitory action of C1-INH

Fig. 15.2 HANE; effects of C1-INH

Predisposing factors

A genetically determined deficiency of an inhibitor of the enzyme C1 esterase (C1-INH) leads to continued complement activation after trauma, and activation of kinin-like substances that cause a sudden increase in capillary permeability (Fig. 15.2). The C4 is consumed and its plasma level falls, but the level of C3 is usually normal.

Clinical features

- Blunt injury is the most consistent precipitating event. The trauma of dental treatment is a potent trigger, and some attacks follow emotional stress.
- Abdominal pain, nausea or vomiting, diarrhoea, rashes and peripheral oedema sometimes herald an attack.
- HANE typically produces acute onset of oedema affecting the lips, tongue, mouth, face and neck region, the extremities and the gastrointestinal tract after minor trauma.
- Oedema may persist for many hours and even up to 4 days and, throughout, involvement of the airway is a constant threat.
- The mortality may be as high as 30% in some families, but the disease is compatible with prolonged survival if emergencies are avoided or effectively treated.

Diagnosis

Diagnosis of hereditary angioedema is from:

- family history
- clinical features with a history of oedema after trauma
- blood tests; low C4, but normal C3 levels, and absence of C1-INH activity. In 85% of cases C1-INH levels are reduced (type 1 HANE), but in 15% C1-INH is present though dysfunctional (type 2 HANE).

Management

Management is with C1-INH replacement, fresh plasma, plasminogen inhibitors, such as tranexamic acid, or androgenic steroids, such as danazol or stanazolol.

Acquired angioedema (AAE)

Acquired angioedema is characterized by painless, non-pruritic, non-pitting swelling of the skin that is classified into two forms:

- AAE-I is associated with other diseases, most commonly B-cell lymphoproliferative disorders. Neoplastic lymphatic tissue consumes C1-INH
- AAE-II is an autoimmune condition – autoantibody is directed against C1-INH.

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16

Angular cheilitis (angular stomatitis)

Key points

- Angular cheilitis affects both commissures
- Most cases are seen in people with denture-related stomatitis
- In other cases, a deficiency state may be the cause
- Treat both the infection (mainly *Candida albicans*) and underlying cause.

Introduction

Angular cheilitis is inflammation typically seen at both commissures (angles) of the lips (Fig. 16.1).

Incidence

Angular cheilitis is common.

Age

It occurs mostly in adults.

Sex

It occurs in both sexes.



Fig. 16.1 Angular stomatitis

Geographic

No known geographic incidence.

Predisposing factors

Angular cheilitis is most often chronic, seen in the elderly, and due to infective and/or mechanical causes. It is predisposed by what are known as the '3Ds' (Fig. 16.2):

- Denture-wearing, denture-related stomatitis and disorders that predispose to candidiasis:
 - dry mouth
 - tobacco smoking.
- Deficiency states, such as:
 - deficiency anaemias
 - iron deficiency
 - hypovitaminoses (especially B)
 - malabsorption states (e.g. Crohn's disease) or eating disorders
 - possibly zinc deficiency, but only rarely
 - defects in immunity, such as in Down syndrome, HIV infection, diabetes, cancer, immunosuppressed people, eating disorders and others.
- Disorders where the lip anatomical relationships are changed – such as when the vertical dimension of occlusion is reduced – or where lips are enlarged, such as in orofacial granulomatosis, Crohn's disease and Down syndrome.

Aetiology

A number of factors (mechanical, infective, nutritional or immunological) may be implicated alone or in combination.

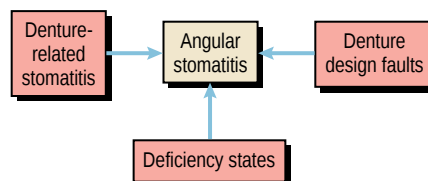


Fig. 16.2 Pathogenesis of angular stomatitis

- Most angular cheilitis is seen in older patients who are wearing a complete maxillary denture beneath which is denture-related stomatitis. Mechanical factors may play a part. As a consequence of ageing, the upper lip overhangs the lower at the angles of the mouth, producing a fold that keeps a small area of skin macerated. Infective agents are probably the major cause.
- Infective agents, mainly *Candida albicans* or *Staphylococcus aureus*, can be isolated in up to 54% of lesions. *Candida albicans* is the most commonly isolated and is typically carried in the saliva, and was probably responsible for some cases of cheilitis attributed to allergy to denture materials – since contamination of denture-material by *Candida* may cause false-positive patch-test reactions. Dry mouth also predisposes to candidiasis.
- Deficiencies of haematinics (factors required for blood formation) or of immunity can also lead to proliferation of *Candida* species and other micro-organisms.
- Angular stomatitis is, very occasionally, an isolated initial sign of anaemia or iron or vitamin deficiency, but then more often there is also ulceration and glossitis.
- Immune deficiency such as in diabetes, Down syndrome, HIV disease or immunosuppressed patients may result in angular cheilitis associated with candidiasis.

Clinical features

- Soreness, erythema and fissuring affect the angles of the mouth symmetrically. Angular cheilitis most commonly presents as roughly triangular areas of erythema and oedema at both commissures. Atrophy, erythema, ulceration, crusting, and scaling may be seen. Lesions occasionally extend beyond the vermilion border onto the skin in the form of linear furrows or fissures radiating from the angle of the mouth (rhagades), mainly in the more severe forms, especially in denture wearers. An eczematous dermatitis may extend some distance onto the cheek or chin as an infective eczematoid reaction or as a reaction to topical medicaments. In long-standing lesions, suppuration and granulation tissue may develop.
- Commonly, there is also associated denture-related stomatitis.
- Rarely, there is also commissural candida-related leukoplakia intraorally.

Diagnosis

- This is usually a clinical diagnosis, made by clinical examination alone. Inspection may reveal palatal erythema caused by associated denture-related stomatitis, usually due to candidiasis. An underlying

nutritional deficiency may be revealed by a depapillated tongue in iron deficiency, a depapillated glossy red tongue in folate deficiency or a reddish-purple depapillated tongue in vitamin B deficiency. Angular cheilitis accompanied by alopecia, diarrhoea and non-specific oral ulcerations, most commonly of the tongue and buccal mucosa, may suggest zinc deficiency. If the cheilitis is unilateral a local cause, such as trauma, or a systemic problem, such as a split papule of syphilis, may be identifiable.

- In all cases of angular cheilitis in wearers of dental appliances, *Candida* should be sought not only in the lesions, but also from the appliance fitting surface. The skin lesions should also be swabbed. Microbial cultures and a haematological workup (blood picture, and assays of levels of serum iron/ferritin, serum vitamin B₁₂ and corrected red blood cell folate) are indicated when systemic involvement is suspected.
- Maceration of the commissural epithelium can also be brought about by habitual licking as a nervous tic, or by sucking on objects (perleche), but this is not true angular cheilitis and the erythema usually extends well beyond the commissural areas and vermillion.

Management

Management of angular cheilitis is sometimes difficult and may need to be prolonged:

- Tobacco habits should be stopped.
- Underlying systemic disease must be sought and treated: a course of oral iron and vitamin B supplements may be helpful in indolent cases.
- If infection is the cause of angular cheilitis, treatment will only be effective if the infection is also treated. Permanent cure can be achieved only by eliminating candidiasis as well as the growth of *Candida* beneath the denture. Recurrence of angular cheilitis must be prevented by eliminating organisms from their reservoir. Dentures should be kept out of the mouth at night and disinfected in a candidacidal solution, such as hypochlorite. Denture-related stomatitis should be treated with an antifungal. Miconazole may be preferable (cream applied locally, together with the oral gel) as it has some Gram-positive bacteriostatic action, but there is a high relapse rate unless treatment is prolonged. Miconazole is absorbed systemically and may occasionally potentiate the action of warfarin, phenytoin and the sulphonylureas. Nystatin or amphotericin (as cream or ointment) should, therefore, be tried first in patients taking these drugs. Angular stomatitis should be treated with a topical antifungal (e.g. miconazole). *Staphylococcus* infection can be cleared with topical antibiotics, such as fusidic acid ointment or cream used at least four times daily.

Mixed infections of *Candida* and *Staphylococcus* respond best to topical miconazole.

- Mechanical predisposing factors should be corrected. A change in dentures may be necessary; new dentures that restore facial contour may help. In rare intractable cases, surgery or, occasionally, collagen injections may be useful in trying to restore normal lip commissural anatomy.

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17

Aphthae (recurrent aphthous stomatitis)

Key points

- Aphthae are multiple recurrent small, round or ovoid ulcers which have circumscribed margins, erythematous haloes, and yellow or grey floors, appearing first in childhood or adolescence.
- A minor degree of immunological dysregulation underlies aphthae.
- Most patients appear otherwise well and predisposing factors are unclear.
- Ulcers similar to aphthae (aphthous-like ulcers) may be seen in some immune disorders.
- Topical corticosteroids control most aphthae.

Introduction

Recurrent aphthous stomatitis (RAS), also known as aphthae or canker sores, is a common condition which is characterized by presenting typically:

- with multiple recurrent small, round or ovoid ulcers which have circumscribed margins, erythematous haloes, and yellow or grey floors (Fig 17.1)
- on non-keratinized and mobile mucosae – they are rare on gingivae or palate
- first in childhood or adolescence.

It is important to note that individual aphthae last only a limited period of time, before they heal: this is quite a different history from ulcers that persist without healing, such as malignant ulcers.

Incidence

RAS affects at least 10% of the population, and the highest prevalence, up to 25%, is in higher socioeconomic classes.

Age

RAS typically starts in childhood or adolescence.

Sex

There is a slight female predisposition to RAS.

Geographic

RAS occurs worldwide though it appears to be most common in the developed world.

Predisposing factors

- There is a genetic predisposition. This is shown by a positive family history in about one-third of patients and by an increased frequency of HLA types (HLA-A2, A11, B12 and DR2).
- There may be a haematinic deficiency. In up to 20% of patients, deficiencies of iron, folic acid (folate) or vitamin B are found. Iron deficiency is usually due to chronic haemorrhage (e.g. from the gastrointestinal or genitourinary tract). Folic acid is found in green leafy vegetables especially, and body stores are small; deficiencies may be dietary, or related to malabsorption or drugs (alcohol, anticonvulsants, carbamazepine, and some cytotoxic drugs). Vitamin B₁₂ is found especially in meat, is absorbed via intrinsic factor from the gastric parietal cells in the ileum and stored in the liver for about 3 years. Dietary deficiency can arise particularly in vegans, in pernicious anaemia and after gastrectomy, and in ileal disease (e.g. Crohn's disease). Histamine H₂ receptor antagonists (cimetidine, ranitidine, omeprazole) can also impede vitamin B₁₂ absorption. In about 3% of patients with RAS, coeliac disease (gluten-sensitive enteropathy) – an allergic reaction to gluten in wheat – is seen.
- Cessation of smoking may precipitate or exacerbate RAS in some cases, but the reason is unclear.
- Stress underlies RAS in some cases and ulcers appear to exacerbate during school or university examination times.
- Trauma from biting the mucosa or from dental appliances may lead to some aphthae.

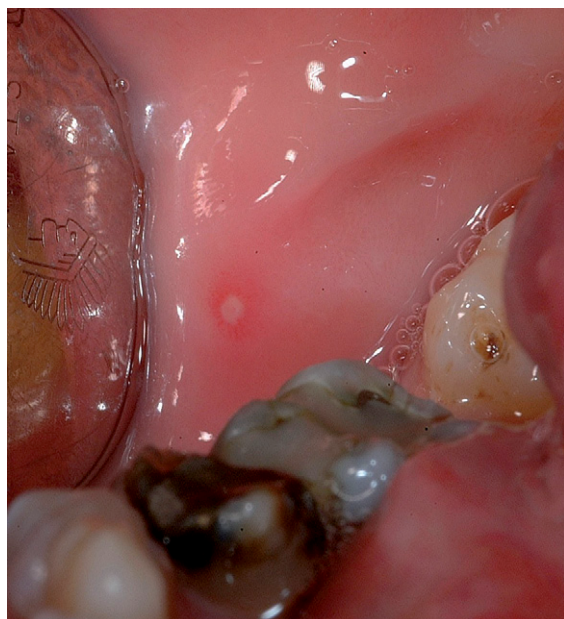


Fig. 17.1 Minor aphthae

- Endocrine factors are relevant in some women where RAS are related to the fall in progestogen level in the luteal phase of the menstrual cycle, or to the contraceptive pill, and then RAS may regress temporarily in pregnancy.
- Allergies to food occasionally underlie RAS, and there is a high incidence of atopy.
- Sodium lauryl sulphate (SLS), a detergent in some toothpastes and other oral healthcare products, may produce oral ulceration.

Aphthous-like ulcers

Ulcers similar to RAS (aphthous-like ulcers) may be seen in:

- immune deficiencies such as HIV, cyclical neutropenia and other immune defects
- drug use, especially non-steroidal anti-inflammatory drugs (NSAIDs) and nicorandil
- Behçet syndrome, where mouth ulcers are seen along with ulcers of the genitals
- periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome in children, which resolves spontaneously and rarely has long-term sequelae. Corticosteroids are highly effective symptomatically; tonsillectomy and cimetidine treatment have been effective in a few patients
- Sweet syndrome, in which mouth ulcers are found with conjunctivitis, episcleritis and inflamed tender skin papules or nodules.

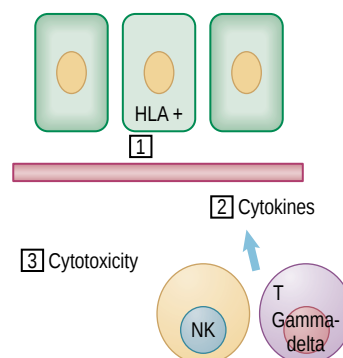


Fig. 17.2 Pathogenesis of aphthae

Aetiology and pathogenesis

The aetiology of RAS is not entirely clear, and aphthae are, therefore, termed 'idiopathic'. There is no evidence that RAS is a classical autoimmune disease, since there is no association with systemic autoimmune disorders, none of the common autoantibodies are found, and RAS tends to resolve spontaneously with increasing age. Also, in most instances the serum immunoglobulin levels are normal.

Indeed, RAS may not be a single condition, but rather may be the manifestation of a group of disorders of quite different aetiology. Despite many studies trying to identify a causal microorganism, RAS does not at present appear to be infectious, contagious, or sexually transmitted.

However, cross-reacting antigens between the oral mucosa and microorganisms may be involved. Reactions to heat shock proteins (HSP) are one possibility. Patients with RAS have circulating lymphocytes reactive with peptide 91-105 of HSP 65-60.

It seems likely that a minor degree of immunological dysregulation underlies aphthae. Immune mechanisms that appear to play a role in a people with a genetic predisposition to oral ulceration include the following (Fig. 17.2):

- T-helper cells (gamma-delta cells), which predominate in the early RAS lesions, along with some natural killer (NK) cells.
- Cytotoxic cells then appear in the lesions and there is evidence for an antibody-dependent cellular cytotoxicity (ADCC) reaction.
- Mononuclear cells, T cells, neutrophils and NK cells may, therefore, be involved.

Clinical features

Patients with RAS have no clinically detectable systemic symptoms or signs; if ulceration affects the genitals or other mucosae, the diagnosis cannot be of RAS alone.

Table 17.1
Clinical characteristics of the different presentations of RAS

	Minor	Major	Herpetiform
Percentage of all aphthae	75–85	10–15	5–10
Size (mm)	2–5	>10	<5
Duration (days)	10–14	>14	10–14
Scarring	No	Yes	No

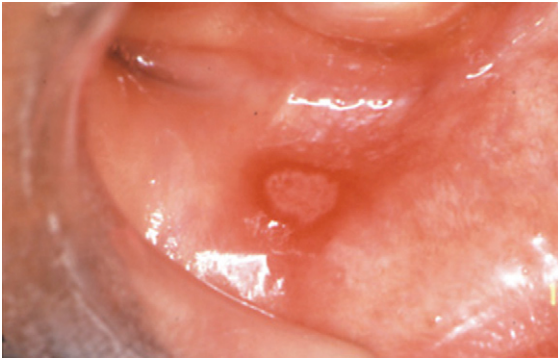


Fig. 17.3 Minor aphthae



Fig. 17.5 Herpetiform ulcers



Fig. 17.4 Major aphthae

There are three main clinical types of RAS (Table 17.1), though any significance of these distinctions is unclear (they could be three distinct disorders):

- Minor aphthous ulcers (~80% of all RAS)
- Major aphthous ulcers
- Herpetiform ulcers.

Minor aphthous ulcers (MiAU; Mikulicz ulcer)

This type of RAS:

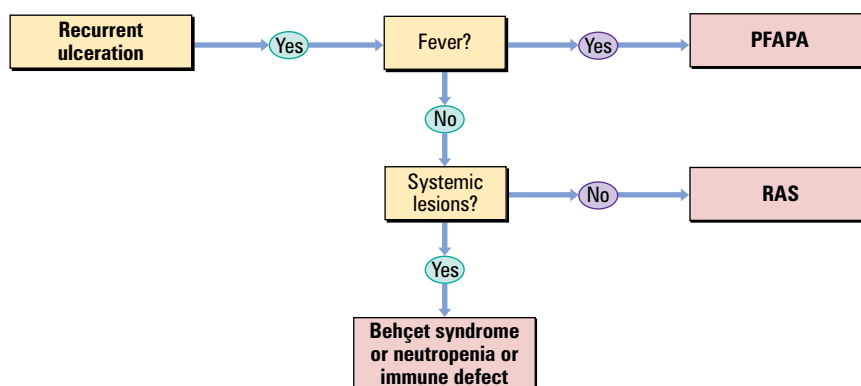
- occurs mainly in the 10–40 year age group
- often causes minimal symptoms

- consists of small round or ovoid ulcers 2–4mm in diameter (Fig. 17.3), in groups of only a few ulcers (1–6) at a time, with initially yellowish floors surrounded by an erythematous halo and some oedema, but the floors assume a greyish hue as healing and epithelialisation proceeds
- affects mainly the non-keratinized mobile mucosae of the lips, cheeks, floor of the mouth, sulci or ventrum of the tongue
- heals in 7–10 days
- recurs at intervals of 1–4 months
- leaves little or no evidence of scarring.

Major aphthous ulcers (MjAU)

This type of RAS, also known as Sutton's ulcers or peradenitis mucosa necrotica recurrens (PMNR):

- are round or ovoid
- reach a large size, usually about 1cm in diameter or even larger
- are found on any area of the oral mucosa, including the keratinized dorsum of the tongue or palate (Fig. 17.4).
- occur in groups of only a few ulcers (1–6) at one time
- heal slowly over 10–40 days
- recur extremely frequently
- may heal with scarring
- occasionally are found with a raised erythrocyte sedimentation rate or plasma viscosity.



Algorithm 17.1 Recurrent ulceration

Herpetiform ulceration (HU)

This type of RAS:

- are found in a slightly older age group than the other RAS
- are found mainly in females
- begin with vesiculation, which passes rapidly into multiple minute pinhead-sized discrete ulcers (Fig. 17.5)
- increase in size and coalesce to leave large, round, ragged ulcers
- involve any oral site, including the keratinized mucosa
- heal in 10 days or longer
- are often extremely painful
- recur so frequently that ulceration may be virtually continuous.

- anti-endomysial, anti-gliadin and transglutaminase antibody assays (positive in coeliac disease).

Management

Patient information sheet

APHTHOUS ULCERS

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- These are common.
- The cause is not known.
- Children may inherit ulcers from parents.
- Aphthous ulcers are not thought to be infectious.
- Some deficiencies or diseases may predispose to ulcers.
- No long-term consequences are known.
- Blood tests and biopsy may be required.
- Ulcers can be controlled, but rarely cured.
- Useful website: <http://www.usc.edu/hsc/dental/opath/Cards/AphthousStomatitis.html>

Diagnosis

Diagnosis of RAS is based on the history and clinical features, as no specific tests are available (Algorithm 17.1). Biopsy is rarely indicated, and is only usually needed where a different diagnosis is suspected. However, to exclude the systemic disorders discussed above, it is often useful to undertake investigations on:

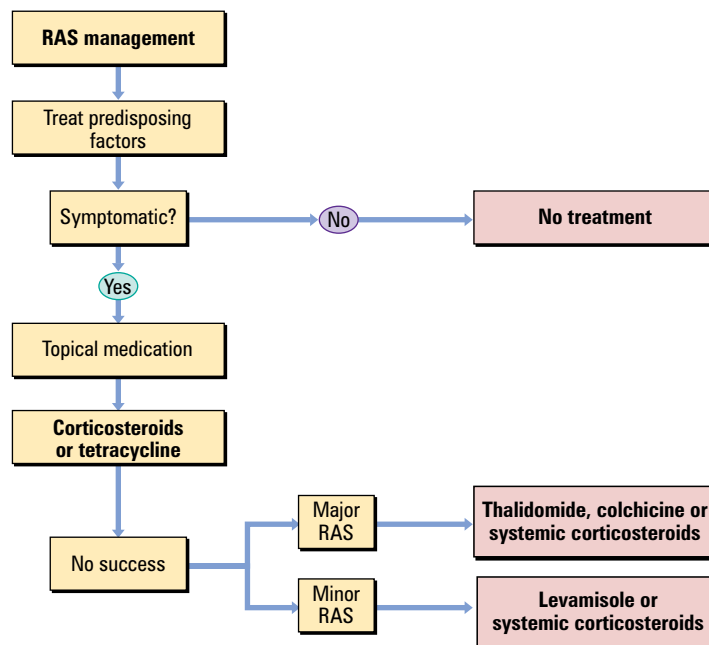
- blood
 - erythrocyte sedimentation rate (or plasma viscosity)
 - a full blood picture
 - haemoglobin
 - white cell count and differential
 - red cell indices
 - red cell folate assay
- serum
 - ferritin levels (or other iron studies)
 - vitamin B₁₂ measurements

Disorders where aphthous-like ulcers are also seen (Table 17.2) should be excluded:

- Behçet's, Sweet's and PFAPA syndromes
- EBV infection
- Immunodeficiency syndromes
- Gastrointestinal diseases, especially coeliac disease and Crohn's disease
- Predisposing factors should be corrected (Algorithm 17.2):
 - ensure patients avoid trauma, avoid hard or sharp foods (e.g. toast, potato crisps) and brush their teeth atraumatically (e.g. by using a small-headed, soft toothbrush)
 - if SLS is implicated, this should be avoided

Table 17.2
Some disorders with aphthous-like ulceration

Disease	Comment
Cyclic neutropenia	Cyclic reduction in circulating levels of neutrophils about every 21 days. Affected patients develop oral ulceration, fever, cutaneous abscesses, upper respiratory tract infections and lymphadenopathy. Other oral complications include severe gingivitis and aggressive periodontitis. Treated with recombinant Granulocyte Colony Stimulating Factor (rG-CSF). Other neutropenias (e.g. chronic neutropenia) can give rise to superficial oral mucosal ulceration without any significant periodicity.
Behçet's disease	Ulceration may be more severe, and patients also have recurrent genital ulceration, cutaneous and ocular disease and other gastrointestinal, neurological, renal, joint and haematological abnormalities.
EBV infection or HIV disease	See Chapters 31 and 39
MAGIC syndrome	Behçet's disease variant (Ch. 42).
PFAPA syndrome	Periodic fever, aphthae like ulceration, pharyngitis and cervical adenitis. Rare, tends to occur in young children, self-limiting, and non-recurrent. May respond to cimetidine (via suppression of T lymphocyte function)
Sweet's syndrome	Acute neutrophilic dermatosis (Ch. 42)



Algorithm 17.2 RAS management

- any iron or vitamin deficiency should be corrected, once the cause of that deficiency has been established
- if there is an obvious relationship to certain foods, these should be excluded from the diet; patch-testing to reveal allergies may be indicated
- the occasional patient who relates ulcers to the menstrual cycle or to an oral contraceptive may benefit from suppression of ovulation with a progestogen, or a change in the oral contraceptive
- causal drugs should be excluded.
- Relief of pain and reduction of ulcer duration.

Fortunately, the natural history of RAS is one of eventual remission in most cases. However, this may take several years and, thus, treatment is indicated if the patient has significant discomfort (Tables 17.3 and 17.4):

- Topical corticosteroids can often control RAS. The major concern of adrenal suppression with long-term

Table 17.3
Treatment regimens for RAS

Treatment	Preparations available	Particularly suitable for
Covering agents	Orabase	Reducing pain
Topical analgesics/ anaesthetics/ anti-inflammatory agents	Benzydamine hydrochloride mouthwash or spray Amlexanox 5% paste	Reducing pain
Topical antiseptics	Doxycycline Chlorhexidine gluconate	Hasten healing
Topical mild potency steroids	Hydrocortisone sodium succinate 2.5mg qid OR Triamcinolone 0.1% in carboxymethylcellulose paste applied to dried areas with moistened finger	Frequently recurring or severe ulcers
Topical moderate potency steroids	Beclomethasone dipropionate aerosol 2 puffs (100 µg) spray onto affected area to a maximum of 8 puffs/day Fluocinonide, clobetasol, or betamethasone sodium phosphate one 0.5mg tablet dissolved in 10ml of water used as a mouthwash qid held in mouth for a minimum of 3 minutes	Inaccessible sites (e.g. soft palate)
Systemic agents	Oral prednisolone 40mg for 5 days, reduce by 5mg every 2 days to 5mg, reduce by 1mg/day until complete OR Colchicine 500 µg/day OR Pentoxifylline 400mg tds OR Azathioprine 50–10mg daily OR Thalidomide 50–200mg qds or bd 3 to 8 weeks	Severe RAS, or aphthous- like ulceration

Children under 6 cannot be expected to rinse and expectorate effectively; avoid preparations that cannot be safely swallowed
Avoid tetracycline preparations, even as a mouthwash, in children under 12

Table 17.4
Therapies for aphthae shown to have benefit in at least one controlled trial

Agent	Main preparations	Route	Daily dose (adults)	Possible main adverse effects/ contraindications
<i>Mild disease</i>				
Amlexanox	5% in adhesive base	Topical	Applied to ulcers 4 times daily*	Stinging
Chlorhexidine	0.12% or 0.2% aqueous mouthwash or 1% gel	Topical	4 times daily*	Superficial tooth staining (reduce coffee, tea, red wine intake)
Corticosteroids	In adhesive base (carmellose), or as pellet, spray or cream	Topical	Applied to ulcers 4 times daily*	Oral candidiasis (recommend adding antifungals to more potent corticosteroids because of this possible risk)
<i>Severe disease</i>				
Corticosteroids	Tablet or capsule	Systemic	Orally 30–60mg**	Bone loss Increases blood pressure Hyperglycaemia Adrenal suppression
Thalidomide	Tablet	Systemic	Orally 50mg*	Teratogenic (contraindicated in pregnancy) Drowsiness Neuropathy (monitor sensory nerve action potentials every 3 months)

*For 2 or more weeks, repeated if ulcers recur.

**1 week treatment, reducing dose over a further week.



Fig 17.6 Minor aphthae on tongue are difficult to manage with pastes

and/or repeated application has rarely been addressed, although the preparations noted below appear not to cause this problem:

- topical hydrocortisone hemisuccinate pellets (Corlan), 2.5mg
- topical triamcinolone acetonide in carboxymethyl cellulose paste (Adcortyl in Orabase), four times daily (difficult to apply to mobile areas such as the tongue; Fig. 17.6)
- stronger topical corticosteroids (e.g. betamethasone sodium phosphate as a 0.5mg tablet dissolved in 15ml water to make a mouth rinse used four times daily).
- Topical tetracycline (a capsule of 100mg doxycycline dissolved in 10ml water) as a mouth rinse may provide relief and reduce ulcer duration, but should be avoided in children under 12 years old who might ingest the tetracycline and develop tooth staining.
- Good oral hygiene should be maintained; chlorhexidine or triclosan mouthwashes may help.
- Anti-inflammatory agents; there is a spectrum of topical agents, such as benzydamine and amlexanox, that may help in the management of discomfort in RAS.
- If RAS fails to respond to these measures, systemic immunomodulators may be required, under specialist supervision. These include:
 - corticosteroids systemically (e.g. prednisolone)
 - levamisole
 - colchicine
 - thalidomide.

Websites

<http://dermnetnz.org/site-age-specific/aphthae.html>
<http://www.usc.edu/hsc/dental/opath/Cards/AphthousStomatitis.html>

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18 Atypical facial pain

Key points

- Atypical facial pain (AFP) is a constant chronic orofacial discomfort or pain, for which no organic cause can be found.
- Patients are often women.
- The pain is poorly localized; pain persists for much or all of the day, and is often of a deep, dull boring or burning type.
- There are often multiple oral and/or other psychogenic related complaints.
- Cognitive behavioural therapy or psychoactive medication may be needed.

Introduction

Atypical facial pain (AFP) is a constant chronic orofacial discomfort or pain, which is defined by the International Headache Society as 'facial pain not fulfilling other criteria'. Therefore, it is a diagnosis reached only by the exclusion of organic disease. It falls into the category of medically unexplained symptoms (MUS), most of which appear to have a psychogenic basis. It must be recognized, however, that a patient in pain may well also manifest psychological reactions to the experience.

Atypical facial pain is often a dull boring or burning type of pain of ill-defined location. Although rarely as severe as trigeminal neuralgia, facial pain is continuous for AFP patients, with few, if any periods of remission. Other characteristics are:

- a total lack of objective signs
- a negative result from all investigations
- no clear explanation as to cause
- poor response to treatment.

Incidence

Atypical facial pain is fairly common, probably around 1–2% of the population suffer from it.

Age

Patients are usually middle-aged or older.

Sex

Patients are often women (~70%).

Geographic

There are no geographic factors implicated.

Predisposing factors

There are often recent adverse life events, such as bereavement or family illness and/or dental or oral interventional procedures.

Aetiology and pathogenesis

The mouth and para-oral tissues have among the richest sensory innervation in the body. Furthermore, a large part of the sensory homunculus on the cerebral cortex receives information from orofacial structures. Right from infancy the mouth is concerned intimately with the psychological development of the individual, and disorders of structures such as the lips, teeth and oral mucosa can hold enormous emotional significance. It is hardly surprising, therefore, that orofacial disorders can result in considerable stress and that there are a range of psychogenic types of orofacial pain, including atypical facial pain.

Positron emission tomography in persons with AFP shows enhanced cerebral activity, suggesting an enhanced alerting mechanism in response to peripheral stimuli. This may lead to the release of neuropeptides and the production of free radicals, causing cell damage, and the release of pain-inducing eicosanoids, such as prostaglandins. Recent studies propose that AFP is an early form of trigeminal neuralgia.

Most sufferers from AFP are otherwise normal individuals who are, or have been, under extreme stress, such

as bereavement or concern about cancer. However, some have personality traits, such as hypochondriasis or neuroses (often depression), and a very few have psychoses.

Clinical features

History

- The pain is mainly in the upper jaw.
- The location of the pain is unrelated to the anatomical distribution of trigeminal nerve innervation.
- The pain is poorly localized, and sometimes crosses the midline to involve the other side, or moves to another site.
- The pain persists for much or all of the day, but does not waken the patient from sleep.
- Pain is often of a deep, dull boring or burning type and chronic.
- There are often multiple oral and/or other psychogenic related complaints, such as:
 - dry mouth
 - bad taste
 - headaches
 - chronic back pain
 - irritable bowel syndrome
 - dysmenorrhoea.
- There is a high level of utilization of healthcare services: there have often already been multiple consultations and attempts at treatment. Chronic pain may lead the patients to undergo dental intervention, but to little avail. Patients may seek conservative dentistry, but this is rarely helpful – often rather to the contrary. The saga of pain may lead the dentist eventually to undertake endodontics or exodontics.
- Patients only uncommonly use analgesics to try and control the pain.
- Pain is accompanied by altered behaviour, anxiety or depression. Over 50% of such patients are depressed or hypochondriacal, and some have lost or been separated from parents in childhood. Many lack insight and will persist in blaming organic diseases (or the clinician!) for their pain.

Examination and investigations

The findings on examination include:

- no erythema, tenderness or swelling in the area
- no obvious odontogenic or other local cause for the pain
- total lack of objective physical (including neurological) signs.

Investigation findings include:

- all imaging studies are negative
- all blood investigations are negative.

Diagnosis

AFP occurs in the trigeminal nerve territory, and the pain may sometimes be as severe as trigeminal neuralgia, but its pattern and quality are different. AFP is usually burning, aching, dull, or crushing, whereas trigeminal neuralgia is characterized by quick episodes of jabbing or lancinating pain. Moreover, an individual AFP attack always lasts longer than a few seconds and usually lasts minutes or hours at least.

AFP is a clinical diagnosis, and requires careful dental and otolaryngologic evaluation, and thorough neurological examination. Examination of the mouth, perioral structures and cranial nerves, and imaging (tooth/jaw/sinus/skull radiography and MRI/CT scan with particular attention to the skull base) to exclude organic disease, such as space-occupying or demyelinating diseases, are important. CT scan of the head has a lower yield than MRI because of its poorer resolution of the brain stem and cranial nerves.

Most orofacial pain is of local cause – especially dental. Only after tests rule out other factors can a diagnosis of AFP be made.

Management

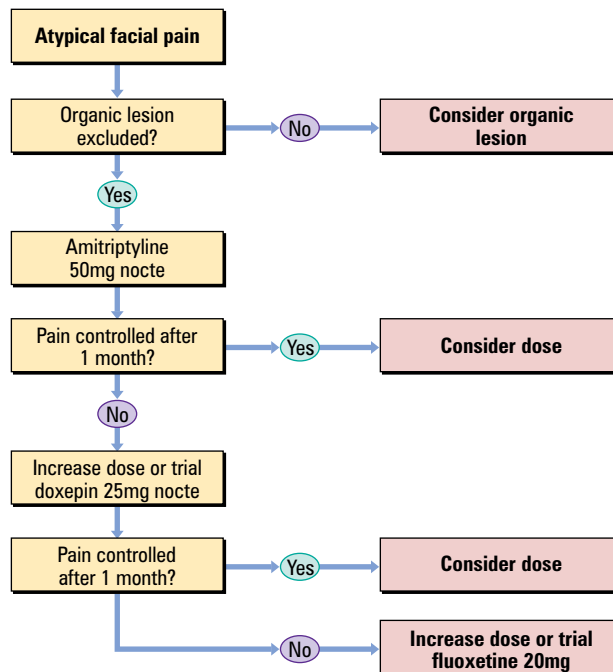
Few patients have spontaneous remission and, thus, treatment is indicated ([Algorithm 18.1](#)).

Patient information sheet

ATYPICAL FACIAL PAIN

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is fairly common.
- The cause is not completely known.
- It is not inherited.
- It may be caused by increased nerve sensitivity.
- There may be a background of stress.
- There are usually no serious long-term consequences.
- X-rays and blood tests may be required.
- Treatment takes time and patience; some nerve-calming drugs can help.
- Useful website: <http://www.facial-neuralgia.org/conditions/atfp.html>



Algorithm 18.1 Atypical facial pain

- Cognitive-behavioural therapy or a specialist referral may be indicated. Patient information is a very important aspect in management.
- A technique termed 'reattribution' helps these patients; it involves demonstrating an understanding of the complaints by taking a history of related physical, mood and social factors, making the patient feel understood and supported, and widening the agenda – thus making the link between the symptoms and psychological problems. It may help explain that depression/tiredness lower the pain threshold and that muscle overactivity and spasm (being 'uptight') causes pain. The physician should:
 - clearly acknowledge the reality of the patient's symptoms and distress and never attempt to trivialize or dismiss them
 - try and explain the psychosomatic background to the problem, ascribing the symptoms to causes for which the patient cannot be blamed
 - set goals, which include helping the patient cope with the symptoms rather than attempting any impossible cure
 - avoid repeat examinations or investigations at subsequent appointments, since this only serves to reinforce illness behaviour and health fears
 - avoid attempts at relieving pain by operative intervention, such as restorative treatment, endodontia or exodontia, since these are rarely successful; indeed, any active dental or oral surgical treatment, in the absence of any specific indication, should be avoided
 - avoid the patient becoming emotionally dependent
- offer referral to a specialist, or a trial of an antidepressant, such as dosulepine, explaining that this is being used to treat the symptoms rather than any depression and that antidepressants have been shown in controlled trials to be effective for this problem, even in non-depressed persons. The pain reduction achieved with antidepressants exceeds that produced by placebos. Also, although antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect, many patients with MUS, such as AFP, show benefit within 1 week.
- Medication used may include one of the following regimens:
 - amitriptyline
 - clonazepam
 - dosulepin
 - doxepin
 - fluoxetine
 - gabapentin
 - nortriptyline
 - trazodone.
- Surgery is not appropriate for treatment of atypical facial pain.

Atypical odontalgia

Atypical odontalgia is pain and hypersensitive teeth in the absence of detectable pathology. The pain is typically indistinguishable from pulpitis or periodontitis

but is aggravated by dental intervention. It is probably a variant of atypical facial pain, and should be managed similarly.

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19 Behçet syndrome

Key points

- Behçet syndrome (BS) is a systemic disease complex manifesting mainly with vasculitis and aphthous-like ulcers.
- HLA-B5101 underlies many cases.
- Diagnosis is on the basis of aphthous-like ulcers plus two or more of recurrent genital ulceration, eye lesions, skin lesions or pathergy.
- Patients with BS need specialist advice and systemic immunomodulation.

Introduction

Behçet syndrome (BS), sometimes also known as Adamantiades syndrome and Behçet's disease, is the association of the triple symptom complex of aphthous-like ulcers with genital ulceration and eye disease (especially iridocyclitis), though a number of other systemic manifestations may also be seen, characterized by necrotizing vasculitis.

Incidence

Behçet syndrome is rare, with an occurrence of one case per 100 000 in the developed world, but the frequency is 10-fold higher in people originating from the eastern Mediterranean countries and Middle East or the 'Silk Road' that Marco Polo followed from there across central Asia to China, Korea and Japan.

Age

Onset of the disease is usually between the ages of 20 and 30 years.

Sex

Behçet syndrome affects twice as many men as women.

Geographic

The disease is found worldwide, but is most common in eastern Asia, China, Korea and Japan. In those countries it is a leading cause of blindness, though this is not the case in the Western world.

Predisposing factors

There are no proven predisposing factors, though at various times foods, such as pork and walnuts, have been suggested. There is a genetic predisposition to Behçet syndrome.

There are associations with HLA-B5 and especially HLA-B51 or its B101 allele in Japan, Korea, Turkey and France, as well as with the ocular manifestations in Britain. HLA-51 may act via ficolin 2 – a lectin that binds to microbial cell surfaces to kill them via complement activation. A significant increase of HLA-A2602 and B3901 in patients without HLA-B51 suggests that these two alleles might also have some secondary influence on the onset of Behçet syndrome. MICA allele is a polymorphic MHC class I related gene A (MICA) family. MICA6 allele, thought to be in linkage disequilibrium with HLA-B51, and recently shown to be significantly associated with Behçet syndrome in Japan and France. ICAM -1 gene polymorphism 469 T/C, may encode risk for Behçet syndrome in Lebanese patients. TNF A -1031*C, -863*A, -857*C and -308*G alleles are significantly associated with BS in Korea. MEFV gene, which is the main factor in familial Mediterranean fever (FMF), is also reported to be a susceptibility gene for Behçet syndrome.

Aetiology and pathogenesis

Behçet syndrome is a vasculitis that has not been proved to be infectious, contagious, or sexually transmitted (Fig. 19.1):

- There are many immunological findings in Behçet syndrome similar to those seen in RAS, with various T lymphocyte abnormalities (especially T suppressor cell dysfunction) and increased polymorphonuclear leukocyte motility.

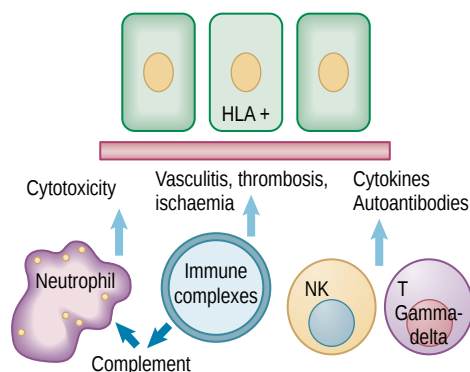


Fig. 19.1 Pathogenesis of Behçet syndrome

- The antigen responsible has not been identified. A viral aetiology (possibly herpes simplex virus) has been proposed and the oral bacterium *Streptococcus sanguis* has been implicated.
- The multiplicity of aetiological factors may have a common denominator in the heat shock proteins (HSP), particularly 65 kDa microbial HSP, which shows significant homology with the human 60 kDa mitochondrial HSP. Indeed, the uncommon serotypes of *Streptococcus sanguis* found in Behçet syndrome cross-react with the 65 kDa HSP, which also shares antigenicity with an oral mucosal antigen. T-cell epitope mapping has identified four peptides derived from the sequence of the 65 kDa HSP that stimulate specifically TCR⁺ lymphocytes from patients with Behçet syndrome. There may be an HLA independent antibacterial host response toward T-helper type 1 immunity mediated by interleukin-12 (IL-12).
- There is increased Th-1 activity, antibody-dependent cellular cytotoxicity to oral epithelial cells and evidence of disturbance of natural killer (NK) cell activity. Cells infiltrating into lesions express interferon (IFN)-gamma, IL-12, IL-18 and tumor necrosis factor alpha (TNF-alpha). Serum levels of IL-6, IL-10 and especially of IL-19, IL-18 and IFN- are seen. Increased proinflammatory cytokines, such as IL-12, are potent inducers of a Th-1 immune reaction.
- Hypercoagulability is a feature. Prostanoid synthesis in endothelial cells or vessel walls is impaired, whereas von Willebrand factor, endothelin-1,2, thromboxane and thrombomodulin are increased and Factor V Leiden and prothrombin mutations are associated with the thrombosis in Behçet syndrome.
- Circulating autoantibodies against a number of components, including intermediate filaments found in mucous membranes, cardiolipin and neutrophil cytoplasm, are present. Circulating immune complexes and changed levels of complement are found, and there is immunoglobulin and complement deposition within and around blood vessel walls and raised levels of acute phase proteins.



Fig. 19.2 Aphthous-like ulcers in Behçet syndrome: the most common feature

- Vasculitis, usually leukocytoclastic vasculitis, is the common denominator in Behçet syndrome; many of the clinical features (erythema nodosum, arthralgia, uveitis) are also common to established immune complex diseases/vasculitis. Immunocytes (mostly CD4 cells), B cells, and neutrophils infiltrate perivascularly. Endothelial dysfunction in vasculitis may be detected by assay of a novel autoantigen Sip1 C-ter.

Clinical features

Behçet's syndrome is a chronic multisystem and sometimes life-threatening vasculitis, characterized mainly by:

- aphthous-like ulcers; in 90–100% of cases (Fig. 19.2). RAS is the most common and usually the initial manifestation of Behçet syndrome. However, only few patients with RAS progress to Behçet syndrome and it is not possible to determine in which patients or when the transition may occur. Recent HLA and immunological findings may eventually help in this respect
- recurrent painful genital ulcers that tend to heal with scars: in 64–88% of cases. Genital ulcers are especially common in females with Behçet syndrome, and resemble RAS
- ocular lesions; uveitis with conjunctivitis (early) and hypopyon (late), retinal vasculitis (posterior uveitis), iridocyclitis and optic atrophy can be present. The most common ocular manifestation is relapsing iridocyclitis, but uveitis, retinal vascular changes and optic atrophy may occur
- CNS lesions are predominantly subtentorial (cerebellum, brainstem and spinal cord), with meningoencephalitis, cerebral infarction, psychosis, cranial nerve palsies, cerebellar and spinal cord lesions, and hemi- and quadriplegia
- skin lesions include erythema nodosum-like lesions, papulopustular lesions and acneiform nodules. Venepuncture is, in some patients, followed by pustulation, but this phenomenon (pathergy), said to be

characteristic of Behçet syndrome, is not seen often in UK or US patients

- involvement of the joints, epididymis, heart, intestinal tract, vascular system and most other systems (though not in every case). Large vein thrombosis (of the inferior vena cava and cranial venous sinuses) can be life-threatening

However, several non-specific signs and symptoms, which may be recurrent, may precede the onset of the mucosal membrane ulcerations by 6 months to 5 years. These include:

- malaise
- anorexia
- weight loss
- generalized weakness
- headache
- perspiration
- decreased or elevated temperature
- lymphadenopathy
- pain of the substernal and temporal regions.

A history of repeated sore throats, tonsillitis, myalgias, and migratory arthralgias without overt arthritis is common.

Diagnosis

Because Behçet syndrome is rare and the symptoms overlap those of many other diseases, it can be very difficult to diagnose.

The International Study Group for Behçet's Disease criteria suggest the diagnosis be made on clinical grounds alone on the basis of aphthous-like ulcers plus two or more of:

- recurrent genital ulceration
- eye lesions
- skin lesions
- pathergy – a >2mm diameter erythematous nodule or pustule forming 24–48 hours after sterile subcutaneous puncture of the forearm skin.

Major criteria for diagnosis of Behçet syndrome include:

- aphthous-like ulcers
- genital ulcers
- ocular lesions
- CNS lesions
- skin lesions.

Minor criteria for diagnosis are:

- arthralgia: large joint arthropathies that are subacute, non-migratory, self-limiting and non-deforming
- superficial or deep migratory thrombophlebitis, especially of the lower limbs. Thromboses of large veins, such as the dural sinuses or venae cavae, can be life-threatening

- intestinal lesions: inflammatory bowel disease with discrete ulcerations
- lung disease: pneumonitis
- renal disease: haematuria and proteinuria.

The major limitation of these diagnostic criteria, however, lies in the fact that recurrent oral ulceration is the key for diagnosis of Behçet syndrome. For example, patients with uveitis and genital ulcers, without oral aphthosis, would not be considered to have Behçet syndrome, although this may in fact be a far-advanced form of Behçet syndrome.

Investigations

Findings of HLA-B5101, raised serum IgD and antibodies to cardiolipin are supportive of a diagnosis of Behçet syndrome.

Disease activity may be assessed by serum levels of acute-phase proteins or antibodies (erythrocyte sedimentation rate, C-reactive protein, α_2 -globulins and other acute-phase reactants) and to intermediate filaments, which are raised in active Behçet syndrome.

Differential diagnosis

This is from other oculomucocutaneous syndromes:

- Sweet syndrome: oral ulcers, conjunctivitis, episcleritis, inflamed tender skin papules or nodules
- Erythema multiforme: erosions, target (iris) lesions
- Pemphigoid: bullae, erosions
- Pemphigus: erosions, flaccid skin bullae
- Reiter syndrome: ulcers, conjunctivitis, keratoderma blenorrhagica
- Ulcerative colitis
- Herpes simplex virus
- Syphilis
- Lupus erythematosus
- Mixed connective tissue disease.

Management

Chronic morbidity is usual in Behçet syndrome; the main problem is ophthalmic involvement, which can result in blindness. The effects of the disease may be cumulative, especially with neurological, vascular and ocular involvement.

Mortality is low, but can occur from neurological involvement, vascular disease, bowel perforation or cardiopulmonary disease, or as a complication of immunosuppressive therapy.

In the face of such serious potential complications, patients with suspected Behçet syndrome should be referred early for specialist advice and typically require systemic immunomodulation. Patient information is also an important aspect in management:

- Topical treatment for RAS includes tetracycline mouthwash and topical corticosteroids
- Systemic treatment includes mainly colchicine
- Other systemic treatments include corticosteroids, azathioprine, ciclosporin, chlorambucil, cyclophosphamide, dapsone, interferon- α , levamisole, rebamipide, thalidomide, etanercept or infliximab.

Websites

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20 Bell's palsy

Key points

- Bell's palsy is an acute face palsy where there is inflammation with demyelination, in the stylomastoid canal.
- Most cases are related to viral infections – mainly herpes simplex virus.
- Management is with antivirals and corticosteroids.

Introduction

The facial nerve carries:

- motor nerve impulses to the muscles of the face, and facial expression, and to the stapedius muscle of the stirrup bone (the stapes) in the middle ear
- secretomotor fibres to the lacrimal (tear) glands, and to the submandibular and sublingual salivary glands
- taste from the anterior tongue (Fig. 20.1) (via the chorda tympani).

Since the function of the facial nerve is so complex, many symptoms may occur if it is disrupted.

Bell's palsy is an acute lower motor neurone paralysis (palsy) of the face:

- No local or systemic cause can be identified except usually herpes simplex virus
- There is inflammation of the facial nerve with demyelination, usually in the stylomastoid canal, and oedema further hazarding the blood supply to the nerve.

Incidence

Bell's palsy represents about 50% of all facial palsies, but is rare at possibly around 10 cases per 100 000 population.

Age

Usually found in the young adult.

Sex

Both sexes can be affected.

Geographic

No geographic factors are known.

Predisposing factors

Predisposing factors, found in a minority of cases, include:

- pregnancy
- hypertension
- diabetes
- a chronic granulomatous disorder, such as Crohn's disease or orofacial granulomatosis, when the association is often Melkersson-Rosenthal syndrome
- lymphoma.

Aetiology and pathogenesis

Bell's palsy is most commonly caused by inflammation and oedema in the facial nerve canal, usually in the stylomastoid canal, causing demyelination of the facial nerve (seventh cranial nerve) (Table 20.1):

- Usually associated with herpes simplex virus (HSV)
- Rarely associated with another infection, such as another herpesvirus:
 - varicella-zoster virus (VZV) infection
 - Epstein-Barr virus (EBV) infection
 - cytomegalovirus (CMV) infection
 - human herpesvirus-6 infection
- A retrovirus:
 - HIV infection
 - HTLV-1 infection
- A bacterium:
 - otitis media
 - *Borrelia burgdorferi* infection (Lyme disease)
- Idiopathic conditions

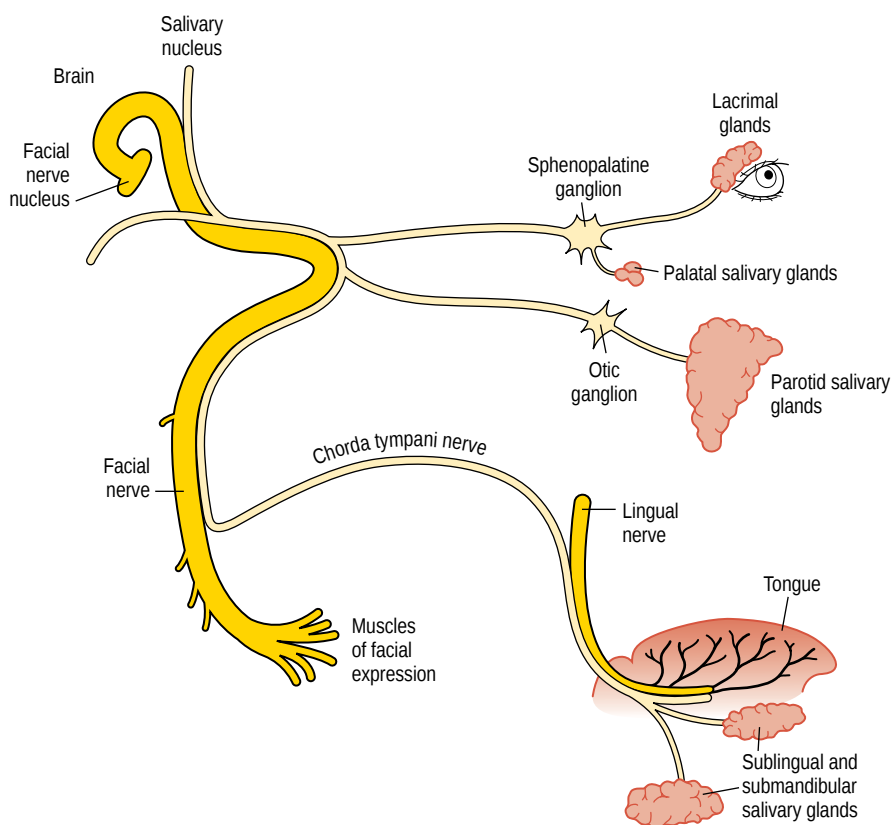


Fig. 20.1 Facial nerve connections

- Disseminated sclerosis
- Kawasaki disease (if this has a microbial cause; see Ch. 43)
- Heerfordt syndrome (Sarcoidosis; Ch. 43)
- Melkersson-Rosenthal syndrome (Ch. 43).

Clinical features

Damage to the facial nerve may result in twitching, weakness or paralysis of the face; in dryness of the eye or the mouth; and/or in disturbance of taste or hearing. There is:

- acute onset of paralysis over a few hours, maximal within 48 hours
- paralysis of the upper and lower face
- usually only unilateral facial paralysis (Fig. 20.2)
- diminished blinking and absence of tearing. Together these can reduce or eliminate the flow of tears across the eyeball, resulting in drying, erosion, and ulceration of the cornea and the potential loss of the eye
- occasionally:
 - pain in the region of the ear or in the jaw may precede the palsy by a day or two
 - there may be complaints of facial numbness, but sensation appears intact on testing

- if the lesion is located proximal to the stylomastoid canal, there may also be hyperacusis (heightened sense of hearing due to reduced damping activity of the stapedius because of loss of function of the nerve to the stapedius) or loss of taste (loss of function of the chorda tympani), or loss of lacrimation.
- a positive family history in up to 10% of patients
- evidence of recurrent episodes in up to 10% of patients.

Diagnosis

The history should be directed to exclude facial palsy caused by other factors, such as:

- stroke
- trauma including surgery (parotidectomy) and lacerations physically affecting the facial nerve (e.g. in the parotid region or to the base of the skull), or by underwater diving (barotrauma)
- tumours affecting the facial nerve (e.g. acoustic neuroma or cholesteatoma)
- inflammatory disorders affecting the facial nerve:
 - multiple sclerosis
 - connective tissue disease

Table 20.1
Localization of site of lesion in, and causes of, unilateral facial palsy

Muscles paralyzed	Lacrima	Hyperacusis	Sense of taste	Other features	Probable site of lesion	Type of lesion
Lower face	N	-	N	Emotional movement retained $\pm$ monoparesis or hemiparesis $\pm$ aphasia	Upper motor neurone	Stroke, brain tumour, trauma, HIV infection
All facial muscles	$\downarrow$	+	$\downarrow$	$\pm$ VIth nerve damage	Lower motor neurone Facial nucleus	Multiple sclerosis
All facial muscles	$\downarrow$	+	$\downarrow$	$\pm$ VIIIth nerve damage	Between nucleus and geniculate ganglion	Fractured base of skull, posterior cranial fossa tumours, sarcoidosis
All facial muscles	N	$\pm$	N or $\downarrow$	-	Between geniculate ganglion and stylomastoid canal	Otitis media, cholesteatoma, mastoiditis
All facial muscles	N	-	N	-	In stylomastoid canal or extracranially	Bell's palsy, trauma, local analgesia (e.g. misplaced inferior dental block), parotid malignant neoplasm, Guillain-Barré syndrome
Isolated facial muscles	N	-	N	-	Branch of facial nerve extracranially	Trauma, local analgesia

N, normal; +, present; $\downarrow$, reduced.



Fig. 20.2 Bell's palsy

- sarcoidosis
- Melkersson-Rosenthal syndrome
- infections affecting the facial nerve:
 - viral infections [HSV, VZV, EBV, CMV, HIV infection, HTLV-1 infection (Japanese and African-Caribbean patients mainly)]
 - bacterial infections [middle ear infections (e.g. otitis media), Lyme disease (camping or walking in areas that may contain deer ticks)].

Bell's palsy is less likely to be the diagnosis if:

- trauma has occurred
- multiple cranial nerves are involved
- there are features consistent with multiple sclerosis
- there are signs of neoplasia
- the paralysis is slowly progressive or chronic.

The examination should include the following:

- A full neurological examination, especially to exclude a stroke, and to exclude lesions involving other cranial nerves (especially the abducens and vestibulocochlear nerves).
- Examination of the facial nerve; weakness is demonstrated by testing the corneal reflex and asking the patient to close the eyes against resistance, raise the eyebrows, raise the lips to show the teeth, and try to whistle.
- Ear and mouth examination to exclude Ramsay-Hunt syndrome; herpes zoster of the facial nerve ganglion (geniculate ganglion), which causes lesions in the palate and ipsilateral ear, and facial palsy.

- Ear examination, for discharge and other signs of middle ear disease.

Investigations that may be indicated include the following:

- A test for the degree of nerve damage; facial nerve stimulation or needle electromyography may be useful, as may electrogustometry, nerve excitability tests, electromyography and electroneuronography.
- A test for loss of hearing; pure tone audiometry is often used.
- A test for taste loss.
- A test for balance.
- A test for tear production – Schirmer’s test, in which a strip of filter paper is placed in the lower conjunctival fornix and the amount of tear production measured.
- Magnetic resonance imaging or computed tomography imaging of the internal auditory meatus, cerebellopontine angle and mastoid may be needed to exclude an organic lesion such as a tumour – particularly in progressive facial palsy.
- Blood pressure measurement to exclude hypertension.
- Blood tests, which may include:
 - fasting blood sugar levels (to exclude diabetes)
 - serological tests for HSV or other virus infections, such as HIV, may need to be considered
 - serum angiotensin converting enzyme levels to exclude sarcoidosis
 - serum antinuclear antibodies to exclude connective tissue disease
 - in some areas, Lyme disease (tick-borne infection with *Borrelia burgdorferi*) should be excluded by enzyme-linked immunosorbent assay (ELISA).
- Occasionally, a lumbar puncture is required.

Management

Most patients with Bell’s palsy (up to 85%) improve spontaneously within a few weeks. However, the after-effects in the remaining 15–40% can be so severe and distressing, that active treatment is warranted. The prognosis can be assessed on several factors:

- Favourable prognostic signs include:
 - incomplete paralysis in the first week
 - persistence of the stapedial reflex, measured by electroneurography.
- Bad prognostic signs include:
 - an initially complete paralysis (then only 50% recover completely within a week, and few who have not recovered by 2 weeks will do so)
 - hyperacusis
 - severe taste impairment

- diminished lacrimation or salivation, especially if in older, diabetic or hypertensive patients.

Treatment with systemic corticosteroids results in 80–90% complete recovery. There is, thus, a strong argument for treating all patients with prednisolone. Since HSV is frequently implicated, antivirals (usually aciclovir or valacyclovir systemically) are also justifiably used. The evidence favours use of aciclovir plus prednisolone if commenced within the first 72 hours of symptom onset.

Patient information is also an important aspect in management. Complications include the following:

- The commonest complication of Bell’s palsy is corneal dryness and scarring due to inadequate eyelid closure. Therefore, during the acute phase, the cornea should be protected with an eye pad. Synthetic tears (hypromellose drops) may help. Protective glasses or clear eye patches are often used to keep the eye moist and to keep foreign materials from entering the eye.
- If paralysis persists and function remains incomplete, the palpebral fissure may narrow, the nasolabial fold deepens and there may be leakage of saliva from the commissure.

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21

Burning mouth syndrome (oral dysaesthesia)

Key points

- Burning mouth 'syndrome' (BMS) is a burning sensation, experienced in the absence of identifiable organic aetiological factors.
- BMS is seen especially in women
- BMS most frequently affects the tongue, with persistent discomfort.
- Management is usually with cognitive behavioural therapy or psychoactive medication.

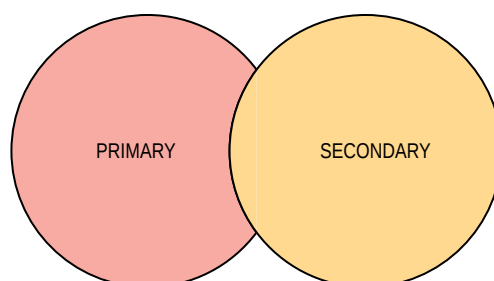


Fig. 21.1 Burning sensation may be primary or secondary

Introduction

A burning sensation in the mouth may be a primary condition, or secondary to identifiable causes (Fig. 21.1). Burning mouth 'syndrome' (BMS) – also known as glosso-pyrosis, glossodynia, oral dysaesthesia or stomatody-nia – is the term used when symptoms described usually as a burning sensation, exist in the absence of identifiable organic aetiological factors: it is a medically unexplained symptom (MUS). The International Association for the Study of Pain define it as:

'A distinctive nosological entity characterized by unremitting oral burning or similar pain in the absence of detectable mucosal changes'

Incidence

BMS is a fairly common chronic complaint, affecting up to five persons per 100 000 population.

Age

BMS is seen especially in middle-aged or elderly patients.

Sex

BMS is seen especially in women, in a ratio of about 3:1.

Geographic

BMS is seen worldwide.

Predisposing factors, aetiology and pathogenesis

- No precipitating cause for BMS can be identified in over 50% of the patients, but in others, local or systemic factors may be identifiable (Fig. 21.2).
- A psychogenic cause, such as anxiety, depression or cancerophobia, can be identified in about 20% of cases.
- In the others, BMS appears to follow either:
 - dental intervention
 - an upper respiratory tract infection
 - use of drugs, such as cytotoxics angiotensin converting enzyme (ACE) inhibitors or protease inhibitors (PIs) (Algorithm 21.1).
 - exposure to various substances (Box 21.1).
- There is no specific relationship to hormonal changes, despite the fact that BMS is often seen in middle-aged or elderly peri- or postmenopausal females.
- Defined clinical conditions that must be excluded, since they can also present with burning, include (Box 21.2):
 - erythema migrans (geographic tongue)
 - lichen planus
 - dry mouth
 - candidiasis
 - glossitis such as may be associated with haematinic (iron, folic acid, vitamin B) deficiency
 - diabetes.

- Organic problems with no detectable clinical lesions that can cause symptoms similar to BMS include:
 - a haematological deficiency state (deficiencies in iron, folic acid or vitamin B) in about 30%
 - restricted tongue space from poor denture construction
 - parafunction, such as nocturnal bruxism or tongue-thrusting

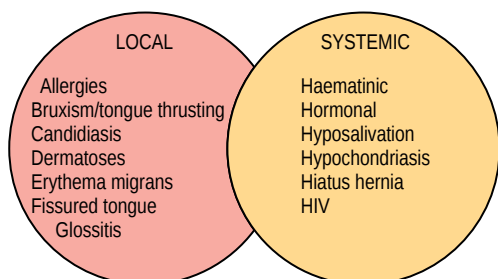
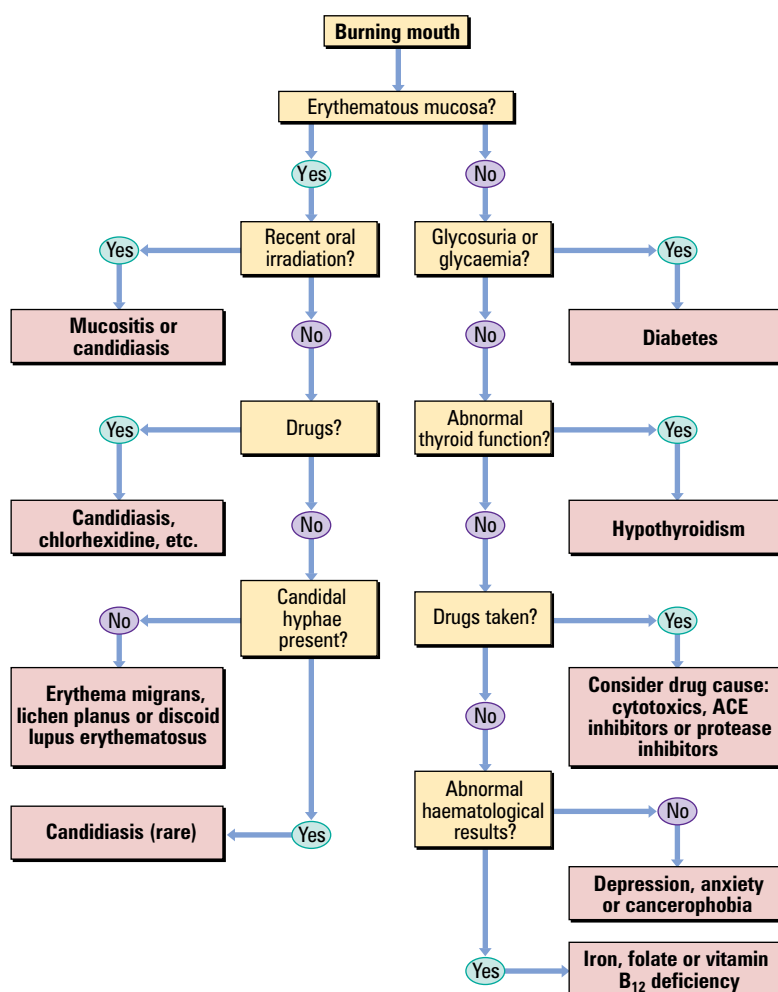


Fig. 21.2 Burning sensation may have local or systemic causes

- neuropathy, such as follows damage to the chorda tympani nerve
- thyroid hypofunction
- drugs.

BMS is increased in frequency in Parkinson's disease and it has been suggested that BMS is a disorder of reduced pain threshold. Patients are often 'super-tasters' – they have raised sensitivity to taste. Hypotheses include that BMS is due to:

- an oral neuropathy and/or neurological transduction interruption induced by salivary compositional alterations or
- changes in the nigrostriatal dopaminergic system, which causes trigeminal excitability (Fig. 21.3) or
- loss of central inhibition from taste damage in the chorda tympani and/or glossopharyngeal nerve (Fig. 21.4) or



Algorithm 21.1 Burning mouth syndrome

Box 21.1

Substances implicated in causing oral burning sensations

Foods and additives

- Benzoic acid
- Chestnuts
- Cinnamonaldehyde
- Instant coffee
- Nicotinic acid
- Peanuts
- Sodium metabisulphite
- Sorbic acid

Metals

- Cadmium
- Cobalt chloride
- Mercury
- Nickel
- Palladium

Plastics

- Benzoyl peroxide
- Bisphenol A
- Epoxy resins
- Methyl methacrylate
- Octyl gallate
- Propylene glycol

Box 21.2

Causes of a burning sensation in the mouth

Local causes

- Allergies
- Bruxism/tongue thrusting
- Candidiasis
- Dermatoses, e.g. lichen planus, dry mouth,
- Erythema migrans (geographic tongue)
- Fissured tongue
- Glossitis

Systemic causes

- Haematinic deficiency of:
 - vitamin B, especially B₁₂
 - folate
 - iron
- Drugs
- Hormonal
- Diabetes
- Hypothyroidism
- Hyposalivation
- Hypochondriasis
- Hiatus hernia
- HIV

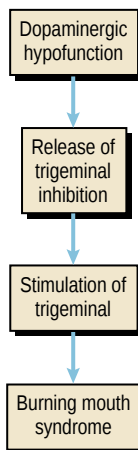


Fig. 21.3 Burning sensation may have a neurological basis

- a sympathetic activity-mediated neuropathic disorder induced by traumatic trigeminal nerve injury or varicella-zoster virus infection.

Clinical features

BMS most frequently affects the tongue, but it can also affect the palate or, less commonly, the lips or lower alveolus. Three types of BMS have been described on the

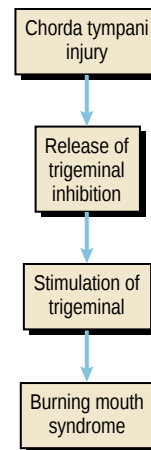


Fig. 21.4 Burning sensation may have a neurological basis

basis of the pattern of symptoms of burning sensation (Table 21.1).

The complaint is:

- variable
 - burning
 - scalded
 - tingling
- moderately severe (visual analogue scale 5–8)
- usually bilateral
- not worsened by eating. Rather it is often relieved by eating and drinking, in contrast to pain caused by

Table 21.1
Types of burning mouth syndrome

Type	Symptom pattern	Frequency	Other features
1	No symptoms on waking, but increasing	Unremitting	–
2	Symptoms on waking and through the day	Most common	Unremitting
3	No regular pattern of symptoms	Least common	May remit

organic lesions, which is typically aggravated by eating. Alcohol may reduce the symptoms

- persistent, but does not disturb sleep
- prolonged >4 months
- rarely spontaneously remits.

There are often multiple oral and/or other psychogenic-related complaints, such as:

- dry mouth
- bad or altered taste
- thirst
- headaches
- chronic back pain
- irritable bowel syndrome
- dysmenorrhoea.

There may be changes in sleep patterns and mood and there have often already been multiple consultations and attempts at treatment. Patients only uncommonly use analgesics to try to control the symptoms.

Diagnosis

Oral examination is important to exclude organic causes of similar discomfort, such as (see [Algorithm 21.1](#)):

- Allergies
- Bruxism/tongue thrusting
- Candidiasis
- Dermatoses such as lichen planus, Dry mouth and
- Drugs such as ACE inhibitors and protease inhibitors
- Erythema migrans (geographic tongue)
- Fissured tongue
- Glossitis such as caused by haematinic deficiency
- Hormonal problems, such as diabetes and hypothyroidism.

Investigations indicated may include psychological screening using, for example, the Hospital Anxiety and Depression (HAD) scale, and laboratory screening in order to exclude:

- anaemia, a vitamin or iron deficiency (blood tests)
- diabetes (blood and urine analyses)

- thyroid dysfunction (blood analyses)
- xerostomia (salivary flow rates)
- candidiasis (oral rinse).

Management

BMS is the diagnosis when all organic causes have been excluded, investigations are all negative, and examination shows no:

- clinically detectable signs of mucosal disease
- tenderness or swelling of the tongue or affected area
- neurological or other objective signs.

About 50% of patients with BMS remit spontaneously within 6 or 7 years, but few have spontaneous remission in the short term, and thus treatment is usually indicated ([Fig. 21.5](#)):

- Patients should avoid anything that aggravates symptoms, such as sparkling wines, citrus drinks and spices. Patient information is an important aspect in management.

Patient information sheet

BURNING MOUTH SYNDROME

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a common condition.
- The cause is not usually known, but it may be a nerve hypersensitivity.
- It is not inherited.
- It is not infectious.
- It may occasionally be caused by some mouth conditions, dry mouth, deficiencies, diabetes or drugs.
- It has no long-term consequences.
- Blood tests or biopsy may be required.
- Burning mouth syndrome may be controlled by some nerve-calming drugs.

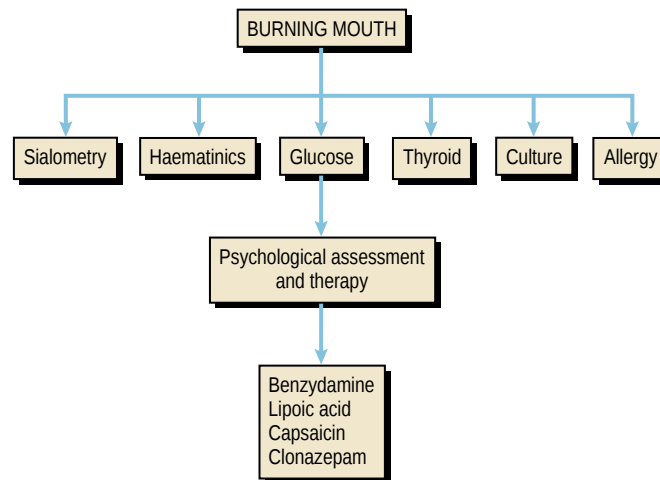


Fig. 21.5 Management of burning sensation

- Reassurance and attention to factors, such as the dentures or haematinic deficiencies, may be indicated.
- Active dental or oral surgical treatment, or attempts at 'hormone replacement', in the absence of any specific indication, should be avoided.
- Cognitive-behavioural therapy or a specialist referral may be indicated. A technique termed 'retribution' helps manage these patients; it involves demonstrating an understanding of the complaints by taking a history of related physical, mood and social factors, making the patient feel understood and supported, and making the link between symptoms and psychological problems.
- It is important to clearly acknowledge the reality of the patient's symptoms and distress and never to trivialize or dismiss them.
- Try and explain the psychosomatic background to the problem, ascribing the symptoms to causes for which the patient cannot be blamed.
- Set goals, which include helping the patient cope with the symptoms, rather than attempt any impossible cure.
- Do not repeat examinations or investigations at subsequent appointments, since this only serves to reinforce illness behaviour and health fears.
- Explain that antidepressants, if prescribed, are being used to treat the symptoms not depression, and that antidepressants have been shown in controlled trials to be effective for this problem, whether or not the patient is depressed. The pain reduction achieved with antidepressants exceeds that produced by placebos, but antidepressants must be given for at least 2–3 weeks to achieve any antidepressive effect. However, most patients with MUS show benefit within 1 week. Medication used includes:
 - amitriptyline
 - clonazepam

- dosulepin
- doxepin
- fluoxetine
- gabapentin
- nortriptyline
- trazodone.

Some patients respond to other medication: topical benzydamine rinse or spray; topical capsaicin cream 0.025% (Zacin) or 0.075% (Axsain); a clonazepam tablet sucked locally; or α -lipoic acid systemically.

Websites

Burning Mouth Syndrome National Organization for Rare Disorders, Inc.
Topic: <http://www.readersdigesthealth.com/kbase/nord/nord234.htm>

Further reading

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22 Cancer

Key points

- Oral cancer is mostly squamous cell carcinoma (OSCC).
- OSCC is seen mainly in older men.
- Risk factors include tobacco, alcohol and betel use.
- Most OSCC affects the lower lip, or margin of tongue.
- OSCC usually manifests as a chronic mucosal lesion.
- Diagnosis needs biopsy confirmation.
- Treatment is with radiotherapy and/or surgery.

Introduction

Cancers of the oral cavity are classified according to site by the International Classification of Diseases (ICD):

- lip (ICD-10, C00),
- tongue (ICD-10, C01, C02) (Fig 22.1)
- gum (ICD-10, C03),
- floor of the mouth (ICD-10, C04),
- unspecified parts of the mouth (ICD-10, C06), tonsil (ICD-10, C09), oropharynx (ICD-10, C10), and other ill-defined sites (ICD-10, C14).

More than 90% of oral cancer is oral squamous cell carcinoma (OSCC) (Box 22.1). OSCC accounts for a large proportion of cancers in the head and neck.

Other malignant oral neoplasms include the following:

- Epithelial malignancies, other squamous carcinomas:
 - arising from a surface (e.g. melanoma)
 - maxillary antral carcinoma (or other neoplasms)
 - glandular (e.g. salivary gland)
 - intrabony epithelial (e.g. odontogenic).
- Secondary carcinomas:
 - within a lymph node (e.g. metastasis from the mouth)
 - within bone (e.g. metastasis from lung, breast, kidney, stomach, liver cancer).
- Sarcomas:
 - in muscle (e.g. rhabdomyosarcoma)
 - in bone (e.g. osteosarcoma)

- in connective tissue (e.g. sarcoma)
- from blood vessels (e.g. Kaposi sarcoma).
- Lymphoreticular neoplasms.
- Lymphomas.

Oral squamous cell carcinoma

Incidence

OSCC is among the 10 most common cancers worldwide. The numbers of new mouth (oral) and oropharyngeal cancers are estimated to be 300 000 cases worldwide, amounting to around 3% of total cancers.

Age

OSCC is seen predominantly in the elderly, but intraoral cancer is increasing, especially in younger adults.

Sex

OSCC is seen predominantly in males, but the male/female differential is decreasing.

Geographic

- There is marked inter-country variation in both the incidence of and mortality from oral cancer.
- In addition, there is also growing evidence of intra-country differences including ethnic differences in incidence and mortality, especially recorded in the UK and USA.
- In the developed world:
 - OSCC is uncommon except in Eastern Europe.
 - The incidence of oral cancer varies between countries and between different regions of the same country. For example, parts of France and Newfoundland have the highest incidence in the West, with about 10 times the incidence of oral carcinoma in the UK. Also, oral cancer is more than twice as common in Scotland than in England and Wales and, even within Scotland, there are regional differences.
- In the developing world, particularly South-East Asia and Brazil:
 - the incidence of oral cancer is the highest in the world, but varies widely in different areas

► Box 22.1

WHO classification of tumours of the oral cavity and oropharynx***Malignant epithelial tumours**

- Squamous cell carcinoma 8070/3
 - Verrucous carcinoma 8051/3
 - Basaloid squamous cell carcinoma 8083/3
 - Papillary squamous cell carcinoma 8052/3
 - Spindle cell carcinoma 8074/3
 - Acantholytic squamous cell carcinoma 8075/3
 - Adenosquamous carcinoma 8560/3
 - Carcinoma cuniculatum 8051/3
- Lymphoepithelial carcinoma 8082/3

Epithelial precursor lesions**Benign epithelial tumours**

- Papillomas 8050/0
 - Squamous cell papilloma and verruca vulgaris
 - Condyloma accuminatum
 - Focal epithelial hyperplasia
- Granular cell tumour 9580/0
- Keratoacanthoma 8071/1

Salivary gland tumours

- Salivary gland carcinomas
 - Acinic cell carcinoma 8550/3
 - Mucoepidermoid carcinoma 8430/3
 - Adenoid cystic carcinoma 8200/3
 - Polymorphous low-grade adenocarcinoma 8525/3
 - Basal cell adenocarcinoma 8147/3
 - Epithelial-myoepithelial carcinoma 8562/3
 - Clear cell carcinoma, not otherwise specified 8310/3
 - Cystadenocarcinoma 8450/3
 - Mucinous adenocarcinoma 8480/3
 - Oncocytic carcinoma 8290/3
 - Salivary duct carcinoma 8500/3

- Myoepithelial carcinoma 8982/3
- Carcinoma ex pleomorphic carcinoma 8941/3
- Salivary gland adenomas
 - Pleomorphic adenoma 8940/0
 - Myoepithelioma 8982/0
 - Basal cell adenoma 8147/0
 - Canalicular adenoma 8149/0
 - Duct papilloma 8503/0
 - Cystadenoma 8440/0

Soft tissue tumours

- Kaposi sarcoma 9140/3
- Lymphangioma 9170/0
- Ectomesenchymal chondromyxoid tumour
- Focal oral mucinosis
- Congenital granular cell epulis

Haematolymphoid tumours

- Diffuse large B-cell lymphoma 9680/3
- Mantle cell lymphoma 9673/3
- Follicular lymphoma 9690/3
- Extranodal marginal zone B-cell lymphoma of MALT type 9699/3
- Burkitt lymphoma 9687/3
- T-cell lymphoma (including anaplastic large cell lymphoma) 9714/3
- Extramedullary plasmacytoma 9734/3
- Langerhans cell histiocytosis 9751/1
- Extramedullary myeloid sarcoma 9930/3
- Follicular dendritic cell sarcoma/tumour 9758/3

Mucosal malignant melanoma 8720/3**Secondary tumours**

*Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded/0 for benign tumours,/3 for malignant tumours and/1 for borderline or uncertain behaviour.

- there are ethnic differences in incidence, often attributed to lifestyle habits.

Potentially malignant (precancerous) conditions include:

Aetiology

Potentially malignant states

Potentially malignant (precancerous) lesions that can progress to OSCC include, especially (Table 22.1):

- erythroplasia (erythroplakia): the most likely lesion to progress to severe dysplasia or carcinoma
- leukoplakia (see Ch. 27):
 - proliferative verrucous leukoplakia
 - sublingual leukoplakia
 - candidal leukoplakia
 - syphilitic leukoplakia

- actinic cheilitis
- lichenoid lesions; cases of dysplasia with a lichenoid appearance (lichenoid dysplasia)
- discoid lupus erythematosus
- submucous fibrosis
- previous oral malignancy
- immunosuppression
- syphilitic glossitis
- dyskeratosis congenita
- Paterson-Kelly syndrome (sideropenic dysphagia; Plummer-Vinson syndrome).

One of the main features that appears to precede the onset of malignancy is epithelial dysplasia, a histological term describing the combination of disorderly maturation

and disturbed cell proliferation. The changes indicative of dysplasia are shown in Box 22.2. Dysplasia varies in severity, and it is the more severe grades that are associated with higher malignant potential. However, dysplasia does not always indicate a malignant potential, since it can also be seen in regenerating tissue and some non-pre-cancerous lesions such as some:

- ulcers
- viral infections
- candidal infections
- granular cell tumours.



Fig. 22.1 Cancer of the tongue (squamous cell carcinoma)

Predisposing factors (risk factors) for OSCC

OSCC appears related mainly to a number of lifestyle factors (Box 22.3):

- In the developed world, OSCC is seen especially in the following groups:
 - tobacco users
 - alcohol users
 - lower socioeconomic groups
 - ethnic minority groups.
- In the developing world, OSCC is seen especially in the following groups:
 - tobacco users
 - alcohol users
 - betel quid users (some 22% of the world's population use betel)
 - lower socioeconomic groups.
- A predisposition to OSCC has been attributed mainly to specific risk factors, such as tobacco (smoking and smokeless) and alcohol (see below). However, dietary factors as well as the existence of genetic predispositions may also play a part, since neither do all tobacco/alcohol users develop cancer, and equally nor do all patients with cancer have these habits. These other factors may include an impaired ability to metabolize carcinogens and/or to repair DNA damaged by mutagens. Individual susceptibility to cancer may

Table 22.1
Potentially malignant oral lesions

Lesion	Aetiological factors	Features
Erythroplasia	Tobacco/alcohol	Flat red plaque
Leukoplakia	Tobacco/alcohol, human papilloma virus	White or speckled plaque
Proliferative verrucous leukoplakia	Tobacco/alcohol	White or speckled nodular plaque
Sublingual keratosis	Tobacco/alcohol	White plaque
Actinic cheilitis	Sunlight	White plaque/erosions
Lichen planus	Idiopathic	White plaque/erosions
Submucous fibrosis	Areca nut	Immobile mucosa
Discoid lupus erythematosus	Idiopathic	White plaque/erosions
Chronic candidiasis	<i>Candida albicans</i>	White or speckled plaque
Syphilitic leukoplakia	Syphilis	White plaque
Atypia in immunocompromised patients	? Papilloma virus	White or speckled plaque
Dyskeratosis congenita	Genetic	White plaques
Paterson-Kelly syndrome (sideropenic dysphagia; Plummer-Vinson syndrome)	Iron deficiency	Postcricoid web

► Box 22.2

Microscopic features of epithelial dysplasia

Disordered cell maturation

- Irregular hyperplasia and/or atrophy
- Keratosis/parakeratosis
- Drop-shaped rete processes
- Irregular stratification
- Disturbed cell polarity
- Premature and individual cell keratinization
- Reduced cell cohesion
- Cell pleomorphism

Disturbed cell proliferation

- Loss of basal cell polarity
- Basal cell hyperplasia
- Increased nuclear/cytoplasmic ratio
- Enlarged nucleoli
- Nuclear hyperchromatism
- Increased mitoses
- Anisonucleosis
- Abnormal mitoses
- Mitoses in stratum spinosum

Tissue changes

- Loss of regular epithelial stratification
- Reduced cell-to-cell cohesion
- Bullous or drop-shaped rete pegs
- Keratin or epithelial pearls

sometimes be explained by a genotype that results in increased carcinogen exposure as a consequence of their carcinogen or procarcinogen metabolism. The list of known carcinogens is long, but many of the most important are aromatic amines (including arylamines and heterocyclic amines). Potential carcinogens may be taken exogenously with full carcinogenic potential (e.g. tobacco and tobacco-contained nitrosamines, or nitrosamines in products such as Toombak) or sometimes they are procarcinogens, i.e. carcinogens may be produced during their metabolism (e.g. acetaldehyde, produced from alcohol by alcohol dehydrogenase, is carcinogenic). In other instances the liver may metabolize carcinogens (e.g. aldehyde dehydrogenase breaks acetaldehyde down).

Risk factors: tobacco

Tobacco smoke is a complex mixture of at least 50 compounds including polycyclic aromatic hydrocarbons such as benzpyrene, nitrosamines, aldehydes and aromatic amines. Tobacco habits have varied effects:

- Cigarette smokers appear to be about five times more likely to develop OSCC than are non-smokers. The precise role of cigarette smoking is surprisingly difficult to define, not least because many heavy smokers also drink alcohol and can have other

► Box 22.3

The lifestyle factors implicated in OSCC

- Tobacco use
- Betel use
- Alcoholic beverages
- A diet poor in fresh fruit and vegetables
- In the case of lip carcinoma, exposure to sunlight

complicating factors. However, studies of those who abstain from such habits (e.g. Mormons, Seventh Day Adventists) have shown a lower incidence of OSCC.

- Bidi is a type of cigarette made of tobacco rolled in a dried temburni leaf. It is smoked in India and is associated with a high incidence of leukoplakia and oral cancer. Reverse smoking – where the lighted end is held in the mouth, as in parts of India – is linked with a high incidence of OSCC of the hard palate, an otherwise unusual site.
- Cigar smoking may predispose to OSCC, and some studies have shown an association with floor of mouth leukoplakia in women smokers.
- Pipe smoking may be associated with nicotinic stomatitis, a benign non-premalignant condition, but there is evidence from some countries that pipe smoking may be associated with a predisposition to OSCC.
- Tobacco-chewing in peoples from parts of Asia, along with a variety of ingredients in a 'betel quid' [betel vine leaf, betel (areca) nut, catechu, and slaked lime, often together with tobacco] appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods (see below).
- Smokeless tobacco, for example, snuff-dipping in women in south-eastern USA who place snuff in the buccal sulcus, has been shown to predispose to gingival and alveolar carcinoma close to where the snuff is placed.

Risk factors: alcohol

Several studies have shown an association between high alcohol consumption and OSCC. Alcoholic beverages may contain carcinogens or procarcinogens, including:

- ethanol; this is metabolized by alcohol dehydrogenase and to some extent by cytochrome p450 to acetaldehyde, which may be carcinogenic
- nitrosamines
- urethane contaminants.

Many alcoholic drinks also contain congeners and some local brews may contain carcinogens that are

probably more responsible for oral cancer than is pure alcohol (ethanol). For example, in parts of France, such as Brittany, there is a close relationship between the consumption of the alcoholic drink Calvados, a pot-stilled spirit, and cancer of the oesophagus and mouth.

There were suggestions, based on a small number of patients, and which have now not been confirmed, that the frequent use of proprietary alcohol-containing mouthwashes over prolonged periods predisposes to oral cancer, but only in those patients who neither smoke nor drink alcohol.

Risk factors: betel quid

- Betel quid is widely used, though contents vary in different parts of the world and cultures. Betel quid can be made up at home or purchased as ready to chew. Once folded, the resulting quid is placed in the mouth, usually the cheek, and gently chewed and sucked sometimes for hours.
- Betel (paan; the leaf, stem or inflorescence of *Piper betel*) leaves are from the betel vine, a relative of the pepper family. Typical contents are spices, tobacco, areca nut and sometimes slaked lime. A large variety of additives may be incorporated. In India, catechu, derived from acacia pods and subquality areca, is a red-brown paste that may also be spread on the leaf. It contains a high concentration of tannins and gives astringency to the mixture. In Malaysia, gambir is a similar substance, paler in colour, made from the leaves and shoots of *Uncaria gambir*. Other additives that may be incorporated include cardamom pods, cinnamon, cloves, melon and cucumber seeds. Alternatively, menthol, camphor, sugar balls, rose water, aniseed, mint essences or syrup may be used, as well as a wide range of spices (fennel, turmeric, saffron, cumin, coriander, nutmeg, ginger). Tobacco is shredded, sun-dried tobacco from *Nicotina tabacum* or *Nicotina rustica*. Tobacco may be used directly in the quid, may be raw, sun dried or roasted, and may be strong or mild in flavour. In addition, roasted tobacco leaves can be finely chopped, powdered and scented for use in the quid, or the leaf residue boiled, made into paste and scented with perfume or rose water. Areca nut (the seed of *Areca catechu*, sometimes referred to as betel nut, although it is from a different plant than the betel leaf) is the seed of the areca palm, is about the size of a nutmeg and has a thick, fibrous husk. Slaked lime (calcium hydroxide) is made from chalk, coral or sea shells, and may be mixed with coconut oil, turmeric water, cream, whey or sugar sweets.

Risk factors: other chewing habits

- Other chewing habits usually involving tobacco and stimulants, are used in different cultures [e.g. Qat (Khat), Shammah, Toombak].

Risk factors: others

- Microorganisms, such as *Candida*, syphilis and human papilloma viruses (HPV), have been detected in some potentially malignant lesions and some OSCC where they may play a role. HPV are especially implicated in tonsillar carcinoma. HPV-16 is particularly implicated.
- Actinic radiation may predispose to lip cancer. Facts that support such a relationship include:
 - lip cancer involves the more exposed lower lip, rather than the upper lip
 - there is a higher incidence of lip cancer in outdoor workers and rural populations than in office workers or urban populations
 - fair-skinned people in sunny climates tend to develop lip cancer more than dark-skinned people (as well as skin cancer and melanoma).
- Immune defects may predispose to OSCC, especially lip cancer. This is increased in, for example, immunosuppressed renal transplant recipients.
- There is concern that cannabis use may predispose to OSCC.
- Diets rich in fresh fruits and vegetables and of vitamin A may have a protective effect on oral cancer and pre-cancer.

Pathogenesis

OSCC arises as a consequence of multiple molecular events causing genetic damage affecting many chromosomes and genes, which leads to DNA changes:

- Genes that are damaged and play crucial roles in carcinogenesis include mainly those involved in cell growth and control:
 - Tumour suppressor genes controlling the fate of chromosomally damaged cells and the cell growth cycle, such as p16 and p53.
 - Oncogenes involved in cell signalling, such as PRAD-1, Int-2, hst-1, bcl-1 and H-*ras*.
 - Genes for enzymes involved in chromosome shortening (telomerases).
- The accumulation of genetic changes leads to cell dysregulation to the extent that growth becomes autonomous and invasive mechanisms develop – this is carcinoma.
- The neoplastic process manifests first intraepithelially (oral intraepithelial neoplasia) near the basement membrane as a focal, clonal overgrowth of altered keratinocyte stem cells, which expand upward and laterally, replacing normal epithelium.
- After some time (sometimes years), invasion of the epithelial basement membrane signifies the start of invasive cancer (Box 22.4). Epithelial cells then proliferate into and invade the underlying tissues (Fig. 22.2).

► Box 22.4

Degrees of epithelial dysplasia and carcinoma

- *Mild dysplasia* Atypical and immature basal cells extend above the basal layers into the lower third of the epithelium
- *Moderate dysplasia* Atypical and immature basal cells extend above the basal layers into the middle third of the epithelium
- *Severe dysplasia* Atypical and immature basal cells extend throughout the epithelium
- *Carcinoma* Atypical and immature basal cells extend throughout the epithelium together with invasion of the lamina propria

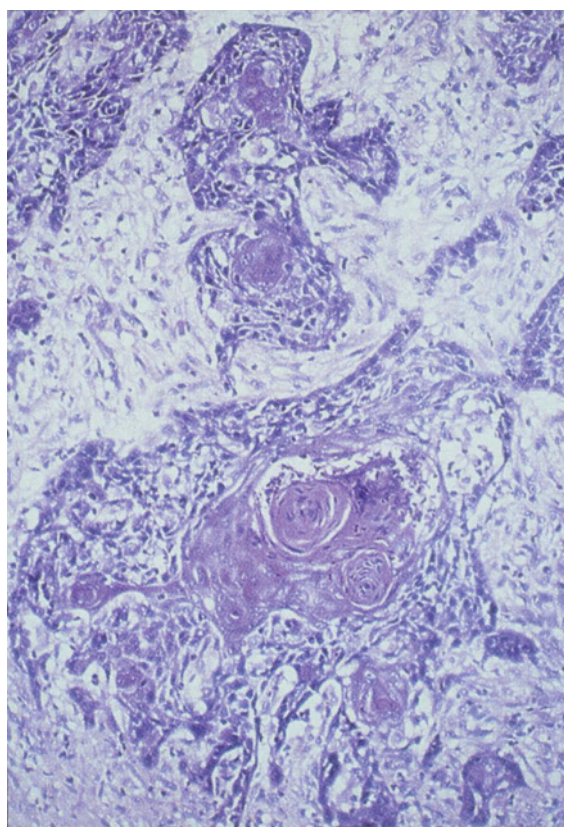


Fig. 22.2 Histopathology of squamous cell carcinoma

Clinical features

OSCC may present clinically as a:

- granular ulcer with fissuring or raised exophytic margins (Fig. 22.3)
- red lesion (erythroplasia)
- white lesion

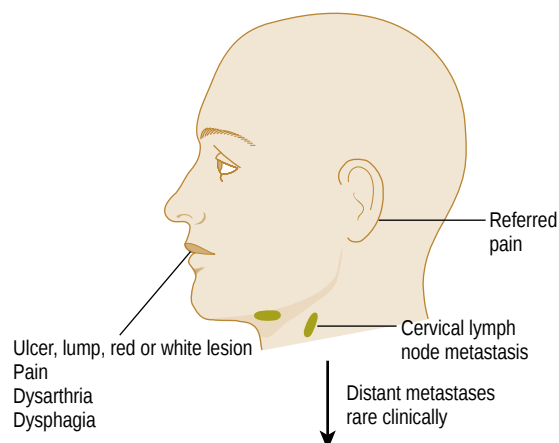


Fig. 22.3 Presenting features of oral carcinoma



Fig. 22.4 Cancer of the tongue

- mixed white and red lesion
- lump, sometimes with abnormal supplying blood vessels
- lump/ulcer which is indurated (i.e. a firm infiltration beneath the mucosa)
- non-healing extraction socket
- lesion fixed to deeper tissues or to overlying skin or mucosa
- lymph node enlargement, especially if there is hardness in a lymph node or fixation. Enlarged cervical nodes in a patient with oral carcinoma may be caused by infection, reactive hyperplasia secondary to the tumour, or metastatic disease. Occasionally, a 'positive' lymph node is detected in the absence of any obvious primary tumour
- second primary neoplasms in the aerodigestive tract may be seen in those with OSCC over 3 years in up to 25%, and in up to 40% of those who continue to smoke
- most oral cancer is carcinoma on the lower lip; the other main site is the posterolateral border/ventrum of the tongue (Fig. 22.4).

Table 22.2
Frequency of carcinoma at different sites

Location	Approx. % of all OSCC	Approx. % of intraoral OSCC
Lip	30	–
Tongue	25	45
Soft palate/trigone area	15	30
Hard palate	5	10
Gingiva	5	10
Buccal mucosa	2	5

Clinical features of lip cancer

- In the developed world, nearly 30% of all oral cancer affects the lip: in some ways this can be regarded as a somewhat different disease to intraoral carcinoma.
- Lip cancer affects mainly the lower lip and has a far better prognosis than intraoral cancers.

Clinical features of intraoral cancer

- Some 25% of OSCC in the developed world affects the tongue, the common intraoral site.
- The majority of OSCC involve the lateral border of the tongue and/or the floor of the mouth, but the very invasive nature of these tumours makes difficult the precise definition of the site of origin. Nevertheless, most arise from the lower part of the mouth (Table 22.2) raising questions as to why this site appears pre-disposed to tumour development. Perhaps carcinogens pool in saliva in this so-called 'graveyard' or 'coffin' area?
- In the developing world, where OSCC arises mainly from betel use, OSCC is most common in the buccal mucosa.
- Most intraoral tumours are larger than 2cm in diameter at presentation.
- Carcinomas in the anterior mouth are usually detected at an earlier stage than are carcinomas of the posterior oral cavity.

Diagnosis

- There should be a high index of suspicion, especially of a solitary lesion present for over 3 weeks: biopsy is invariably indicated. Clinicians should be aware that single ulcers, lumps, red patches or white patches, particularly if any of these are persisting for more than 3 weeks, may be manifestations of frank malignancy.
- The whole oral mucosa should be examined as there may be widespread dysplastic mucosa ('field change')

or even a second neoplasm, and the cervical lymph nodes must be examined. Frank tumours should be inspected and palpated to determine the extent of spread.

- Examination under general anaesthetic may be indicated for patients with:
 - tumours in the posterior tongue
 - tumours where the margins cannot be readily defined
 - an enlarged cervical node but no visible primary neoplasm. Blind biopsy of the tonsil or fossa of Rosenmuller may then be indicated. Positron Emission Tomography (PET) may also be helpful to identify latent primary neoplasms.
 - any suggestion of a second primary tumour (SPT) who may then need panendoscopy of larynx, pharynx and oesophagus.
- OSCC should be staged according to the TNM (Tumour, Node, Metastases) classification of the International Union against Cancer – according to tumour size, nodal metastases and distant metastases (Box 22.5) – since this classification relates well to overall survival rate (i.e. the earlier the tumour, the better the prognosis and the less complicated and mutilating is the treatment).

Investigations

When deciding which investigations to undertake, three principles should be adhered to:

- Confirm the diagnosis histopathologically, and determine if there is malignant disease elsewhere, whether there are:
 - bone, muscles or cervical lymph nodes involved
 - other primary tumours (typically in the upper aerodigestive tract – mouth, nares, pharynx, larynx, oesophagus). There is controversy as to the need for endoscopy in all cases to detect such tumours
 - metastases, which initially are to regional lymph nodes and later to liver, bone and brain. Imaging may detect abnormalities that escape clinical examination.
- Ensure that the patient is as prepared as possible for the major surgery required, particularly in terms of their understanding and consent, general anaesthesia, potential blood loss and ability to metabolize drugs.
- Address any potential dental or oral problems preoperatively, to avoid later complications, such as osteoradionecrosis.

These three principles almost invariably indicate the following investigations:

- Lesional biopsy
- Biopsy or fine needle aspiration of equivocal neck lymph nodes

► Box 22.5

TNM classification of malignant neoplasms***Primary tumour size (T)**

Tx	No available information
T0	No evidence of primary tumour
Tis	Only carcinoma in situ
T1, T2, T3, T4	Increasing size of tumour†

Regional lymph node involvement (N)

Nx	Nodes could not be or were not assessed
N0	No clinically positive nodes
N1	Single clinically positive homolateral node less than 3cm in diameter
N2	Single clinically positive homolateral node 3–6cm in diameter, or multiple clinically positive homolateral nodes, none more than 6cm in diameter
N2a	Single clinically positive homolateral node 3–6cm in diameter
N2b	Multiple clinically positive homolateral nodes, none more than 6cm in diameter
N3	Massive homolateral node(s), bilateral nodes or contralateral node(s)
N3a	Clinically positive homolateral node(s), one more than 6cm in diameter
N3b	Bilateral clinically positive nodes
N3c	Contralateral clinically positive node(s)

Involvement by distant metastases (M)

Mx	Distant metastasis was not assessed
M0	No evidence of distant metastasis
M1, M2, M3	Distant metastasis is present. Increasing degrees of metastatic involvement, including distant nodes

*Several other classifications are available, e.g. STNM (S = site)

†T1, maximum diameter 2cm; T2, maximum diameter 4cm; T3, maximum diameter >4cm; T4, massive tumour >4cm diameter, with involvement of antrum, pterygoid muscles, base of tongue or skin

- Jaw radiography (often rotating pantomography), though this is inadequate to exclude bone invasion
- Chest radiography or computed tomography (CT). This is important as a preanaesthetic check, especially in patients with known pulmonary or airways disease, and to demonstrate second primary tumours or metastases to lungs or hilar lymph nodes, ribs or vertebrae
- Magnetic resonance imaging (MRI) or CT of the primary site, of the head and neck, and suspected sites of distant metastases, and MRI scans of the neck to delineate the extent of cervical node metastases. Some units routinely examine the chest and abdomen. MRI is particularly useful to determine:
 - tumour spread
 - bone involvement

- nodal metastases
- Electrocardiography
- Blood tests:
 - Full blood picture and haemoglobin
 - Blood for grouping and cross-matching
 - Urea and electrolytes
 - Liver function tests.

In selected cases other investigations may be indicated:

- Bronchoscopy, if chest radiography reveals any lesions
- Endoscopy of the upper aerodigestive tract, especially if there is a history of tobacco use
- Gastroscopy, if a PEG (perendoscopic gastrostomy) is to be used for feeding

- Liver ultrasound, if there is hepatomegaly or abnormal liver function
- Doppler duplex flow studies, in planning radial free forearm flaps
- Angiography, in planning lower limb free flaps.

Molecular and DNA techniques are being introduced for prognostication in potentially malignant lesions and tumours, and to identify nodal metastases. Bacteriological investigations may be indicated.

Biopsy

An incisional biopsy is invariably required. An excisional biopsy should be avoided, since this is unlikely to have excised an adequately wide margin of tissue if the lesion is malignant, but will have destroyed clinical evidence of the site and character of the lesion.

The most appropriate site to biopsy can be difficult to decide. Since red rather than white areas are most likely to show dysplasia, a biopsy should be taken of the former. Various attempts to clinically highlight probably dysplastic areas before biopsy (e.g. by the use of toluidine blue dye or fluorescence) have, unfortunately, not always proven to be reliable, but may be of some help where there is widespread 'field change'.

Some authorities always take several biopsies at the first visit in order to avoid the delay and aggravation resulting from a negative pathology report in a patient who is strongly suspected to be suffering from a malignant neoplasm.

The biopsy should be sufficiently large to include enough suspect and apparently normal tissue to give the pathologist a chance to make a diagnosis and not have to request a further specimen. Most patients tolerate (physically and psychologically) one biopsy session, although it is never a particularly pleasant experience. Most biopsy wounds, whether 0.5cm (too small) or 1.5cm long (usually adequate) heal within 7–10 days. Therefore, it is better to take at least one ample specimen.

Carcinoma is diagnosed when there is:

- dysplasia extending through the full thickness of the epithelium
- extension of the rete pegs into the underlying lamina propria (i.e. invasion across the basement membrane).

It is generally accepted that prognosis is best in early carcinomas, especially those that are well differentiated (Box 22.6, Table 22.3); fortunately, most OSCC is well- or moderately differentiated.

If the pathology report denies malignancy, and yet clinically cancer is still the diagnosis, then the pathology should be re-checked and a re-biopsy may be indicated.

Suspect lymph nodes are best biopsied by needle biopsy, using a fine-bore needle to aspirate cells for cytological examination. False-negative results are possible, but the danger of incisional biopsy is that it may seed malignant cells into the wound. In practical terms ipsilateral enlarged regional lymph nodes in a patient with an obvious oral carcinoma are likely to include metastases (or at least micrometastases) and will need treatment.

► Box 22.6

Grades of carcinoma

Carcinoma	Histopathological features
Well-differentiated	Elongated rete pegs invading lamina propria, with keratin pearls
Moderately differentiated	Irregular invading rete pegs; loss of cellular cohesion
Poorly differentiated	Sheets of invading epithelium with no obvious architecture, but severe cellular abnormalities, such as pleomorphism and hyperchromatism

Table 22.3
Prognosis for intraoral carcinoma

Stage	TNM	Approx. survival at 5 years (%)
I	T1 N0 M0	85
II	T2 N0 M0	65
III	T3 N0 M0 T1, T2 or T3 N1 M0	40
IV	Any T4, N2, N3 or M1	10

Adapted from Sciubba (2001)

Management

Patient communication

Patient communication and information are important aspects in management. One of the most difficult clinical situations in which clinicians find themselves is with the patient in whom serious disease, such as cancer, is suspected. If the patient is to be referred for a diagnosis and insists (rightly) on a full explanation as to why you need to refer for a second opinion, it is unwise for you to suggest a serious diagnosis to the patient. Better that you admit ignorance about the field and say that you are trained more to be suspicious, but doubt the lesion is anything to worry about, though you would be failing in your duty if you did not ask for a second opinion. That is what you would do for a member of your family – why should the patient be treated any the less?

Cancer to many, if not most, patients is a term that forebodes disaster – not unreasonably, since most have had relatives or friends who have died of the disease. The prognosis, at least of intraoral carcinoma, is not especially good, but little is gained by expressing this to the patient or relative. On the other hand, early lesions in otherwise healthy patients, especially those in sites such as the lip, have such a good prognosis that they can be said to be 'curable'. You must leave discussion of actual treatment and prognosis to the surgeon/oncologist concerned, as only they are in a position to give accurate facts to the patient concerned. If you are concerned, phone a specialist or fax, e-mail or write for an urgent opinion.

If a cancer diagnosis has been established, it is reasonable to discuss with the patient, their partner and relatives that:

- tumours differ in their degree of malignancy
- their tumour has been detected at an early stage (hopefully)
- treatment is continually improving
- you have referred them to the best possible centre for treatment
- the oncological team will provide fuller details of treatment options.

Treatment planning

Cancer treatment and planning decisions are based on:

- tumour size, nodal status and metastases
- wishes of the patient
- social circumstances
- co-existent medical conditions.

Cancer treatment and planning involves a multidisciplinary team (MDT) that includes a range of specialties: surgeons, anaesthetists, oncologists, nursing staff, dental staff, nutritionists, speech and physiotherapists, and others. The

MDT should plan the cancer treatment, but must also plan to avoid postoperative complications – this includes planning oral and dental care. Discussions regarding restorative and surgical interventions required before cancer treatment, including osseointegrated implants and jaw reconstruction, are valuable in the planning phase. Oral care is especially important when bisphosphonates are used or radiotherapy is to be given, since there is a liability complications (see Ch. 41), and a risk of osteonecrosis – the initiating factor for which is often trauma, such as tooth extraction, or ulceration from an appliance, or oral infection. As much as possible of dental treatment should be completed before starting cancer treatment.

Treatment modalities

- OSCC is now treated largely by surgery and/or radiotherapy to control the primary tumour and metastases in the draining cervical lymph nodes. Consensus guidelines to treatment are now being published. Combined clinics are needed to agree treatment policy, and offer the best outcomes. Treatment should be planned with a balance in mind between:
 - length of survival
 - quality of remaining life.
- Lip cancer is treated mainly surgically.
- Intraoral cancers <4cm in diameter may be treated equally effectively by surgery or radiotherapy.
- T1 tumours are generally managed surgically.
- T2 tumours are also generally managed surgically. However, tumours of the lateral margin of tongue may be treated by radiotherapy using external beam (40 Gray) plus radioactive iridium implants (25–30 Gray). For many patients, the treatment must include treatment of the lymph nodes in the neck and thus often the treatment of choice is surgery (tumour excision with radical neck dissection), together with radiotherapy.
- T3 tumours are generally treated by surgery followed by radiotherapy if there is extracapsular spread or multiple lymph node involvement. For many patients, the treatment must include treatment of the lymph nodes in the neck and thus often the treatment of choice is surgery (tumour excision with radical neck dissection), together with radiotherapy.
- T4 tumours may be treated with chemo-radiotherapy. Drugs used include cisplatin, fluorouracil (5-Fu) taxanes and methotrexate. TPF is a common regimen (taxane platinum, 5-Fu).

Surgery

Principles

The principles of cancer surgery are to:

- remove the whole tumour:
 - ablative surgery excises the cancer with at least a 2cm margin of clinically normal tissue, to try and ensure no tumour remains



Fig. 22.5 Tracheostomy

- radical neck dissection, for the same reason, removes also the internal jugular vein, lymphatics and accessory nerve, as well as the cervical sensory nerves and the sternomastoid, omohyoid and often digastric muscles. 'Functional' neck dissection, preserving such vital structures is gaining popularity; moderate-dose radiotherapy is, therefore, sometimes used to 'sterilize' such necks of residual cancer cells
- retain as much normal anatomy and function as possible
- permit normal breathing – tracheostomy (Fig 22.5) may be necessary
- support alimentation – often via nasogastric tube or a PEG (Fig 22.6)
- reconstruct to produce acceptable function and cosmetics. Reconstruction from both the operator's and the patient's and family's viewpoint, is best performed at the time of initial surgery, but must be tailored to the patient's ability to cope with a long operation (up to 10 hours or more) and the risk of significant morbidity. For soft tissue reconstruction, local flaps (e.g. nasolabial flaps) can repair small defects. Distant flaps are required to repair larger defects; these include:
 - free flaps: microvascular surgery facilitates excellent reconstruction at a single operation using, for example, forearm flaps based on radial vessels which are particularly useful to replace soft tissue, or those based on the fibula where bone is required
 - pedicle flaps: myocutaneous or osteomyocutaneous flaps based on a feeding vessel to muscle and perforators to the skin paddle, for example flaps based on the pectoralis major, latissimus dorsi or trapezius are now used in a one-stage operation to replace skin and, since they also contain muscle, they have adequate bulk to repair defects and may also be used to import bone (usually rib)
- hard tissue: mandibular defects are reconstructed with implants to maintain aesthetics and anatomy temporarily until the patient is tumour free and bone grafting possible. Bone is traditionally taken as free non-vascularized bone grafts from the iliac

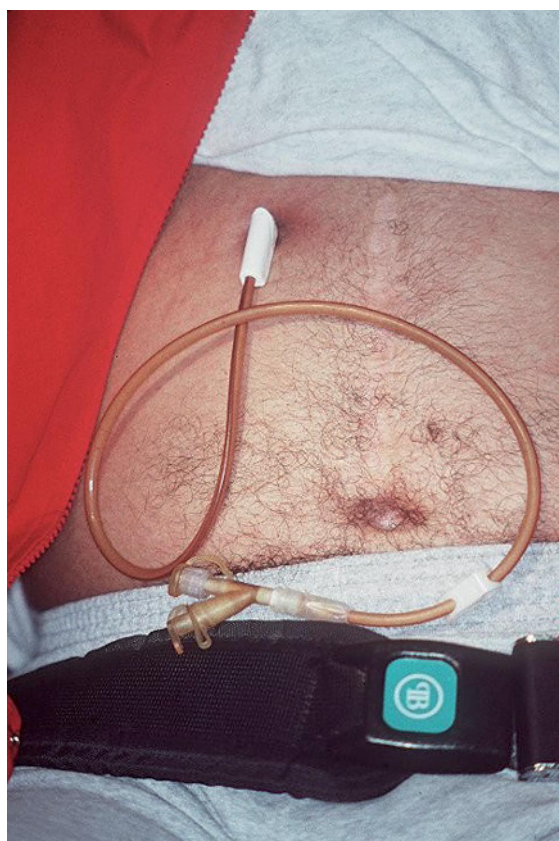


Fig. 22.6 PEG (per-endscopic gastrostomy)

crest or rib, but these often show poor survival in a contaminated area like the mouth, or in a relatively avascular field after irradiation. An osteomyocutaneous flap, such as a fibula graft, greatly improves the vascular bed for the graft, but is time consuming and requires considerable expertise. Maxillary defects are reconstructed with an obturator (bung), which has the advantage that the cavity can be readily inspected.

Surgical complications

- Carotid artery infection and rupture
- Salivary fistula
- Chylorrhoea.

Advantages and disadvantages of surgery

Advantages of surgery include the possibilities of:

- complete tumour and lymph node excision with full histological examination
- removal of involved bone
- use for radio-resistant tumours.

Disadvantages of surgery are mainly that it is mutilating for very large tumours and there is, in any event, perioperative mortality and morbidity, but modern techniques

have significantly decreased these and the aesthetic and functional defects.

Radiotherapy

Principles

Radiotherapy may be used as the sole treatment modality for primary oral cancers without obvious lymph node involvement and also for inoperable tumours.

Radiotherapy typically involves:

- electromagnetic radiation 60KeV to 25MeV from:
 - deep X-rays or linear accelerator
 - radionuclide (e.g. cobalt 60) decay.

Occasionally therapy involves:

- particulate radiation using:
 - electrons
 - neutrons or
 - protons.

Dosage is expressed in terms of absorbed dose:

- Gray (Gy) = energy absorption of 1 joule/kg (1Gy = 100rads).

Radiotherapy can be given by different techniques:

- Interstitial therapy (brachytherapy; plesiotherapy) uses a radiation source close to tumour and is suitable only for small tumours less than 2cm in size and certain sites. Implants placed into the lesion for a few days give a radiation dose equivalent to that from teletherapy, but confined to the lesion and immediate area. Interstitial implants use:
 - iridium-192
 - gold-198 or
 - caesium-137
 - Dose is 65–70 Gy over 5.5–8 days.
- External beam radiation (teletherapy), is accompanied by side-effects more commonly than is brachytherapy. In older times orthovoltage (up to 300kV) was used – X-rays of low penetration with maximal skin dose and high bone absorption and serious adverse sequelae. Teletherapy now uses supervoltage radiation (1–4MeV+) which penetrates and is not particularly absorbed by bone, and the dose is fractionated in order to increase the differential effect on the tumour:
 - most fractionation is treatment once daily, 5 days a week
 - treatment for 3–6 weeks seems optimal
 - standard treatment is 55Gy in 20 fractions over 4 weeks.
- Teletherapy modifications designed to increase tumouricidal effect and reduce adverse effects, include:
 - altered fractionation (hyperfractionation). CHART (continuous hyperfractionated accelerated radiation therapy) is a very accelerated schedule which overcomes the repopulation problem but allows

limited time for reoxygenation, so a hypoxic-cell sensitizer may be especially beneficial: nimorazole is such an agent and has a significant effect in oral cancer

- intensity-modulated radiation therapy (IMRT or conformational or 3D radiation) uses computer-controlled X-ray accelerators to deliver precise radiation doses to cancer, minimizing exposure of normal tissues. This spares the major salivary glands and can improve the post-treatment quality of life
- concomitant cytotoxic agents
- neutron therapy
- hyperbaric oxygen.

Advantages and disadvantages of radiotherapy

Advantages of radiotherapy include the facts that:

- normal anatomy and function are maintained
- general anaesthesia is not needed
- salvage surgery is still available if radiotherapy fails.

Disadvantages of radiotherapy may include mainly that:

- subsequent surgery is more difficult and hazardous and survival further reduced
- failure is probably because of repopulation and hypoxia
- cure is uncommon for large tumours
- adverse effects are common (see Ch. 41).

Rehabilitation

Cancer patients are typically concerned primarily with ridding themselves of the tumour, but aesthetics and restoration of dignity and function are also very important. Feeding can be a problem and it may be necessary to feed via perendoscopic gastrostomy (PEG) or an indwelling central venous (Hickmann) line. Attention is also required to speech, swallowing, oral hygiene and appearance, with prostheses, implants or camouflage in some cases. Physiotherapy is often required.

Prognosis of intraoral carcinoma

Intraoral cancer should be one of the most readily detected neoplasms because of the easy access for clinical and biopsy examination, yet the prognosis is still little better than for lung cancer, i.e. an overall 5-year survival of only about 30%.

Factors influencing prognosis include the following:

- Tumour factors:
 - Increasing stage, depth of infiltration, size of tumour and presence of metastases adversely affect prognosis. Thus the prognosis for stage I tumours is around 85% 5-year survival, but this figure

plummets to 10% in stage IV tumours (Table 22.3). Patients still present for treatment after inordinate delays. Most present at a stage (stage II) when tumours are relatively advanced in size (T2 or more, see Box 22.5), but when there is little clinical evidence of local metastases to lymph nodes and only rarely are distant metastases detectable.

- Lymph node factors (invasion, capsular rupture, nodal site, number of involved nodes). Nodal involvement decreases cure rates by around 50%.
- Histological factors:
 - Tumour grade; well-differentiated tumours appear to have a better prognosis than poorly differentiated or anaplastic carcinomas.
 - Tumour thickness; deep tumours have a worse prognosis.
 - Quality of surgical margins (whether excision margins are tumour free); if the margins are tumour free, prognosis is better.
- The site of the tumour. The prognosis is better where the cancer does not involve the floor of mouth, alveolus, posterior tongue or maxilla.
- Patient factors. The prognosis is usually worse for:
 - male gender: possibly because of the somewhat later presentation of males for treatment, or because of associated medical problems. Many male patients with oral cancer are heavy smokers and drinkers, and some have cirrhosis and nutritional defects
 - age: the poor general health of some aged patients may limit their resistance to the disease or its treatment.
- Treatment factors: the major impact that treatment has had on the prognosis of oral cancer to date has been in relation to improved anaesthetic and medical care. Apart from the general improved expertise of surgical, anaesthetic and medical care, reconstructive surgery and radiotherapy techniques and after-care have been significantly improved.

Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is not a common tumour in Europe or the USA:

- NPC is prevalent in Chinese, North Africans and Inuits.
- It is almost certainly caused by Epstein-Barr virus and other cofactors (environmental and genetic), possibly nitrosamines from smoked fish.
- The tumour usually starts high in the nasopharynx and, because it does not occlude the pharynx to produce symptoms and is very inaccessible to casual inspection, frequently presents late and with a poor prognosis.

- The tumour usually presents in one or a combination of the following ways:

- Causing unilateral loss of hearing on the same side (ipsilateral) by invading and blocking the Eustachian tube. This causes pain, paraesthesiae, or sensory loss in the ipsilateral face – by infiltrating the mandibular division of the trigeminal nerve (Trotter syndrome).
- With cervical lymph node enlargement due to metastases. NPC is a common cause of a malignant cervical lymph node where no primary tumour is obvious, and, therefore, a node biopsy and thorough ear, nose and throat examination and biopsy of the fossa of Rosenmuller are required.

Websites

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Key points

- *Candida* species are common mouth commensals
- *Candida* proliferates if the local ecology changes or if immune defences fall.
- Candidiasis manifests with red or white lesions and soreness.
- Treatment includes correcting the local ecological factors, and/or improving immune defences, together with antifungal medication.

Introduction

Some 50% of the normal population harbour (carry) *Candida albicans* as a normal oral commensal (without disease) and are termed 'Candida carriers'.

Candida carriage

- *C. albicans* resides particularly on the posterior dorsum of tongue.
- *Candida* carriage is more frequent in:
 - women
 - people:
 - of blood group O and with non-secretion of blood group antigens in saliva
 - on high carbohydrate diets causing acidic saliva
 - with xerostomia
 - on broad-spectrum antimicrobial use (e.g. tetracyclines)
 - who wear dental appliances
 - who smoke tobacco
 - who are immunocompromised, such as those with HIV disease, malignancy, Down syndrome, malnutrition or diabetes
 - who are hospitalized.

Host defences

The host defences against *Candida* species include the following:

- Oral epithelium: a physical barrier.
- Microbial interactions: competition and inhibition by the oral flora.

- Salivary non-immune defences: mechanical cleansing plays a major role. Other factors include:
 - lysozyme (muramidase) – can damage *Candida*, stimulate phagocytosis and agglutinate *Candida*
 - lactoferrin – is antifungal and antibacterial due to binding of iron or altering yeast cell wall permeability
 - lactoperoxidase – is anticandidal via multiple factors (H_2O_2 and halides)
 - salivary glycoproteins antigenically similar to blood group antigens – affect adherence to mucosa
 - salivary histatins
 - antileukoprotease
 - salivary histidine-rich polypeptides
 - calprotectin.
- Immune defences, which include:
 - T cells and phagocytes. Polymorphonuclear leukocytes (PMNL) and macrophages phagocytose and produce cytokines, such as: myeloperoxidase, tumour necrosis factor (TNF), interferon- γ (IFN- γ), nitric oxide and granulocyte-macrophage colony stimulating factor (GM-CSF).
 - The full expression of phagocyte effectiveness is dependent on augmentation by cytokines synthesized or induced by T cells, such as lymphokines and IFN- γ .
 - Salivary sIgA antibodies – which aggregate organisms and/or prevent adherence.

Pathogenicity

Candida species are able to colonize and in some circumstances, invade epithelia (Fig. 23.1). Factors implicated in candidal pathogenesis include their:

- enzymes:
 - phospholipases
 - lysophospholipases
 - aspartyl proteinases (secretory aspartyl proteinases – SAP)
 - activating the kallikrein-kinin system
- cell-wall mannans and glycans, which may impair PMNL chemotaxis, phagocytosis, respiratory burst, T lymphocyte reactivity and the macrophage secretion of TNF
- adherence ability: extracellular polymeric material, including mannoprotein and adhesions, such as HWP1 originating from the yeast cell surface, appear important in making hyphal forms adhere more strongly than do yeast forms

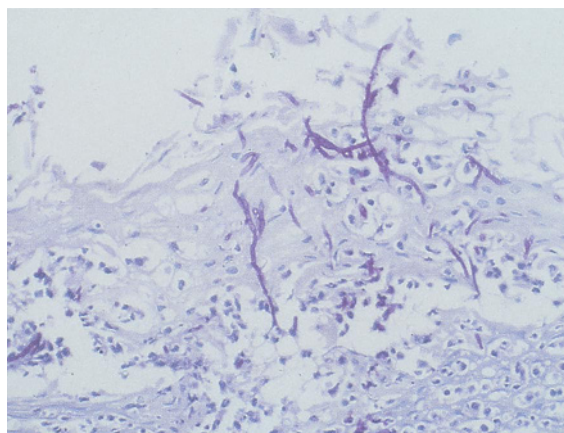


Fig. 23.1 Candidal hyphae stained with periodic acid–Schiff, seen penetrating the epithelium

- Colony switching; *C. albicans* can switch frequently and reversibly between several variant, heritable, phenotypes associated with changes in micromorphology, physiology and virulence.

Candidiasis

Candidiasis (candidosis; moniliasis) is the state when *Candida* species cause lesions:

- The importance of *Candida* has increased greatly, particularly as the HIV pandemic extends since, when host defences are compromised, *Candida* typically colonizes mucocutaneous surfaces and these can be portals for entry into deeper tissues.
- *C. albicans* is the only common cause of oral fungal or yeast infection.
- The most dominant oral species, in decreasing order of frequency, are:
 - *C. albicans*
 - *C. tropicalis*
 - *C. glabrata*
 - *C. parapsilosis*
 - *C. krusei*
 - other *Candida* species
 - other genera which are rare and transient.
- Species other than *C. albicans* (especially *C. krusei*) are increasingly seen in infections, especially in persons with compromised immunity.
- Antifungal resistance is an increasingly serious clinical reality.

Symptomatic candidiasis presents as mainly:

- white lesions (thrush, candidal leukoplakia and chronic mucocutaneous candidiasis), in which hyphal forms are common

► Box 23.1

Factors predisposing to oral candidiasis

- Local factors influencing oral immunity or ecology, including:
 - xerostomia
 - smoking
 - broad-spectrum antimicrobials
 - corticosteroids
 - dental appliances
 - irradiation involving the mouth or the salivary glands
- Systemic immune defects, such as those caused by:
 - extremes of age
 - malnutrition
 - cytotoxic chemotherapy
 - immune T-cell defects, especially HIV infection, leukaemias, lymphomas and cancer, and PMNL defects, such as in diabetes and immunosuppressant drugs
 - anaemia.

- red lesions (denture-related stomatitis, median rhomboid glossitis, erythematous candidiasis), in which yeast forms predominate, and which may be symptomless, although antibiotic stomatitis and angular cheilitis can cause soreness.

Factors that can increase the liability to candidiasis include those that increase carriage, such as (Box 23.1):

- Local factors influencing oral immunity or ecology, including:
 - xerostomia
 - smoking
 - broad-spectrum antimicrobials
 - corticosteroids
 - dental appliances
 - irradiation involving the mouth or the salivary glands
- Systemic immune defects, such as those caused by:
 - extremes of age
 - malnutrition
 - cytotoxic chemotherapy
 - immune T-cell defects, especially HIV infection, leukaemias, lymphomas and cancer, and PMNL defects, such as in diabetes and immunosuppressant drugs
 - anaemia.

Candida serotypes

C. albicans can be differentiated serologically into A and B serotypes, equally distributed in healthy individuals, but there is a significant shift to type B in immunocompromised patients.

► Box 23.2

Classification of oral candidiasis

Primary oral candidiasis (group I)

- Acute: pseudomembranous, erythematous
- Chronic: pseudomembranous, erythematous
- Candida-associated lesions

Secondary oral candidiasis (group II)

- Oral manifestations of systemic mucocutaneous candidiasis (due to diseases such as thymic aplasia and candidiasis endocrinopathy syndrome)
- Hyperplastic plaque-like, nodular
- Denture-related stomatitis, angular stomatitis, median rhomboid glossitis

Classifications of candidiasis

By tradition, the most frequently adopted classification of oral candidiasis has been into (Box 23.2):

- acute candidiasis:
 - pseudomembranous candidiasis (thrush)
 - atrophic candidiasis
- chronic candidiasis:
 - hyperplastic candidiasis
 - atrophic candidiasis
 - hyperplastic candidiasis, which was further subdivided into four groups based on localization patterns and endocrine involvement as follows: chronic oral candidiasis (*Candida* leukoplakia); candidiasis endocrinopathy syndrome; chronic localized mucocutaneous candidiasis; and chronic diffuse candidiasis.

A newer classification categorizes candidiasis into:

- primary oral candidiasis, which is confined to oral and perioral tissues
- secondary oral candidiasis, which is distributed in other parts of the body as well as the oral cavity.

Diagnosis of candidiasis

Diagnosis can, if necessary, be supported by:

- identification of blastospores and pseudohyphae in stained smears from a lesion
- culture, usually on Sabouraud's or dextrose Sabouraud's medium
- occasionally by histology stained by periodic acid-Schiff (PAS).

However, the diagnosis of candidiasis in most instances is clinical and investigations can be complicated by the facts that:

- up to about 50% of the population are carriers
- any attempt at quantitation of *Candida* is affected by time of sampling and the way in which the specimen is handled.

See the relevant clinical presentations described below.

Other investigations

- Tests of immune function are indicated mainly in HIV disease or chronic mucocutaneous candidiasis.
- Since some endocrine disorders may be associated with chronic mucocutaneous candidiasis, tests of thyroid, parathyroid and adrenocortical function are warranted in selected individuals.
- Since oral candidiasis is occasionally associated with nutritional deficiencies or blood dyscrasias, estimates of haemoglobin, white blood cell counts, corrected whole blood folate, vitamin B₁₂ and serum ferritin can be important.

Management of candidiasis

Few patients have spontaneous remission unless the condition is solely related to, for example, the use of an antimicrobial, or a topical corticosteroid, and thus, in other cases, treatment is often indicated. Often, in the treatment of fungal infection, attention to the underlying cause will avoid the need for prolonged or repeated courses of treatment. Intermittent or prolonged topical antifungal treatment may be necessary where the underlying cause is unavoidable or incurable.

Treatment includes the following measures:

- Avoid or reduce smoking.
- Treat any local predisposing cause, such as xerostomia.
- Improve oral hygiene; chlorhexidine has some anticandidal activity.
- Antifungals:
 - Topical antifungal agents are useful for most lesions restricted to the oral cavity and are available as suspensions, tablets and creams. Oral suspensions are useful for patients with dry mouth who may have difficulty in dissolving tablets. Available preparations include: nystatin oral suspension or pastilles, amphotericin lozenges, miconazole gel or tablets, fluconazole tablets or suspension.

- Systemic antifungals are increasingly used, especially fluconazole, but may interact with anti-HIV and other medications.

See the relevant clinical presentations described below.

Prophylaxis of candidiasis

- In patients with severe immunosuppression, prevention of colonization and infection is the goal because the oropharyngeal region may be the primary source of initial colonization and allow subsequent spread of the infection.
- Those at greatest need for such prophylactic antifungals include patients:
 - with HIV disease
 - receiving cancer chemotherapy
 - on immunosuppressive therapy
 - on prolonged antibiotic therapy.

Clinical presentations of candidiasis

The most common form of oral candidiasis is denture-related stomatitis, and sometimes this is complicated by angular stomatitis, again often a *Candida*-related lesion. Candidiasis is not uncommon in neonates, as they have yet to develop acquired immunity, but was rare in older persons before the advent of immunosuppressive therapies and HIV/AIDS. The latter has also highlighted the other red, or erythematous, forms of oral candidiasis. The various types are now discussed in more detail.

Denture-related stomatitis

Denture-related stomatitis is discussed in Chapter 24.

Angular stomatitis

Angular stomatitis (perleche, angular cheilitis) is discussed in Chapter 16.

Thrush

Thrush is the common title for acute pseudomembranous candidiasis, and is so termed because the white flecks resemble the appearance of the breast of the bird of that name.

Incidence

Neonates, who have yet to develop immunity to *Candida* species, may develop thrush, but it is otherwise uncommon in healthy individuals. It is far more common in immunocompromised persons; thrush is a 'disease of the diseased'.

Age

Can occur at any age.

Sex

It can occur in either sex.

Geographic

Candidiasis is seen worldwide.

Predisposing factors

Predisposing factors include changes in local or systemic immunity in the mouth. Thrush in most patients is related to antibiotic or corticosteroid use, or xerostomia. However, if these local factors cannot be identified, systemic disease should be suspected – mainly immune defects, such as in terminally ill patients, leukaemia and other malignancies, HIV disease and patients on immunosuppressive treatment.

Aetiology and pathogenesis

- Thrush is mainly caused by *C. albicans* but, in infants, *C. parapsilosis* is frequently found.
- *C. albicans* adhere to the epithelial surface via extracellular polymeric material, including mannoprotein and adhesins and then hyphae invade the superficial epithelium and penetrate, as far as the stratum spinosum, by liberation of enzymes, such as phospholipases, lysophospholipases and aspartyl proteinase.
- Activation of the kallikrein-kinin system and other factors result in an inflammatory response in the connective tissue comprising lymphocytes, plasma cells and other leukocytes. PMNL migrate into the epithelium in defensive mode, but candidal cell-wall mannans and glycans may impair PMNL chemotaxis, phagocytosis and the respiratory burst.
- The plaques in oral thrush are made up of necrotic material, *Candida* and desquamated parakeratotic epithelia. Oedema and micro-abscesses containing PMNL are found in the outer layers of epithelium. The deeper parts of the epithelium show acanthosis and sometimes even dysplasia.

Clinical features

Thrush is classically an acute infection, but it may persist for many months or even years in patients using corticosteroids topically or by aerosol, in HIV-infected individuals, and in other immunocompromised patients.



Fig. 23.2 Thrush showing white and red lesions

Thrush is characterized by:

- white papules on the surface of the oral mucosa. These may form confluent plaques that resemble milk curds (Fig. 23.2). These can be wiped off with gauze to reveal a raw, erythematous and sometimes bleeding base
- complications, which may sometimes be lesions of the mucosa of the upper respiratory tract and the oesophagus, a combination particularly prevalent in HIV-infected patients.

Diagnosis

The diagnosis of thrush is usually clinical and straightforward, but it has been overdiagnosed in the past. In immunosuppressed patients, a Gram-stained smear should be taken to distinguish it from the thrush-like plaques produced by opportunistic bacteria. Hyphae seem to indicate that the *Candida* are acting as pathogens.

Management

Possible predisposing causes should be looked for and dealt with, if possible. Topical polyene antifungals such as nystatin or amphotericin, or imidazoles such as miconazole or fluconazole are often indicated. With the increasing use of antimycotic therapy, especially in HIV disease, there is a shift towards antifungal-resistant *C. albicans*, as well as the appearance of novel species, such as *C. dubliniensis*, but also towards other species, such as *C. glabrata* and *C. krusei*.

Chronic hyperplastic candidiasis

Chronic hyperplastic candidiasis, or candidal leukoplakia is a persistent white lesion (Fig. 23.3), characterized histologically by parakeratosis and chronic intraepithelial inflammation with fungal hyphae invading the superficial layers of the epithelium.



Fig. 23.3 Chronic hyperplastic candidiasis

Incidence

It is uncommon.

Age

It is found in adults.

Sex

It can occur in either sex.

Geographic

It can be found worldwide.

Predisposing factors, aetiology and pathogenesis

- *C. albicans* is the species by far the most commonly isolated.
- Candidal leukoplakia may be predisposed to in a minority of patients by:
 - smoking
 - iron and folate deficiencies
 - defective cell-mediated immunity
 - blood group secretor status.
- The epithelium of some leukoplakias is invaded by *Candida* hyphae, but it is unclear whether the yeasts are secondary invaders or are causally involved in the development or transformation of leukoplakia. The cellular changes often include hyperplasia, but cellular atypia, mild or severe dysplasia and ultimately in situ or invasive carcinoma may arise.
- The *Candida* biotypes associated with leukoplakias differ from those isolated from normal oral cavities and those from non-homogeneous leukoplakias such as candidal leukoplakia have higher nitrosation potentials, which might indicate a possible role of specific types in the malignant transformation of some leukoplakias.

Clinical features

- Candidal leukoplakias are chronic, discrete raised lesions that vary from small, palpable, translucent, whitish areas to large, dense, opaque plaques, hard and rough to the touch (plaque-like lesions). Homogeneous areas or speckled areas can be seen, which do not rub off (nodular lesions).
- Candidal leukoplakias are non-homogeneous 'speckled' leukoplakias in up to 50%.
- Candidal leukoplakias usually occur on the buccal mucosa on one or both sides, mainly just inside the commissure (Fig. 23.3), less often on the tongue.

Diagnosis

Candidal leukoplakias can be indistinguishable from other leukoplakias except by biopsy when *Candida* hyphae can be seen after staining with periodic acid-Schiff (PAS). Candidal leukoplakia should, therefore, be biopsied both to:

- distinguish it from other non-candidal lesions
- examine for possible dysplasia.

Management

From 9% to 40% of candidal leukoplakias may develop into carcinomas.

Factors influencing the prognosis may include:

- risk factors, such as tobacco and alcohol use
- whether the lesion is speckled (more dangerous) or homogeneous
- the presence (more dangerous) and degree of epithelial dysplasia
- the management adopted.

In order to improve the prognosis:

- tobacco and alcohol habits should be stopped
- antifungals should be used. The lesions of candidal leukoplakia may prove poorly responsive to polyene

antifungal drugs and, in some cases, respond only to systemic fluconazole or itraconazole

- excision is indicated if there is more than mild dysplasia
- the patient should be fully informed about the condition, and reviewed regularly.

Chronic mucocutaneous candidiasis

Chronic mucocutaneous candidiasis (CMC) is the term given to the group of rare syndromes in which there is persistent mucocutaneous candidiasis that responds poorly to topical treatment. Specialist care is indicated (Table 23.1):

- In many patients with persistent oral candidiasis however, no local cause or underlying defect can be identified. In general, the more severe the candidiasis and the more widespread the sites involved, the greater is the likelihood that an immunological defect (particularly of cell-mediated immunity) can be identified.
- A defect of cytokine production (interleukin-2 and IFN- γ) in response to candidal and some bacterial antigens, with reduced Th1 lymphocyte function and enhanced Th2 activity (and increased interleukin-6), and reduced serum levels of IgG2 and IgG4 may be found in some patients with CMC.

CMC syndromes are sometimes familial and present early in life, and one type (candidiasis endocrinopathy syndrome) is associated with autoimmune endocrinopathies, especially hypoparathyroidism, and hypoadrenocorticism (polyendocrinopathy syndrome type I).

Erythematous candidiasis

Erythematous or atrophic candidiasis is candidiasis presenting as red lesions. These may be seen in denture-related stomatitis, antibiotic-induced stomatitis, sometimes in median rhomboid glossitis and, in HIV infection, may develop *de novo*, may precede pseudomembranous

Table 23.1
Chronic mucocutaneous candidiasis

Type	Inheritance	Clinical features
Localized CMC	Sporadic	Persistent oral candidiasis, oesophagitis, iron deficiency
Diffuse CMC (<i>Candida</i> granuloma)	AR or sporadic	Severe chronic oral candidiasis, granulomas, susceptibility to bacterial infections
Candidiasis–endocrinopathy syndrome	AR	Mild chronic oral candidiasis, pernicious anaemia, hypoparathyroidism, hypoadrenocorticism, diabetes, vitiligo, thyroid disease
Candidiasis thymoma syndrome	Sporadic	Chronic oral candidiasis, myasthenia gravis, polymyositis, aplastic anaemia

candidiasis, or may arise as a consequence of persistent acute pseudomembranous candidiasis when the pseudomembranes are shed. Chronic multifocal oral candidiasis is the term used when several persistent red lesions occur.

Denture-related stomatitis

Denture-related stomatitis (denture sore mouth; chronic atrophic candidiasis) consists of mild inflammation of the mucosa beneath a denture, usually a complete upper denture (see Figs 24.1 and 24.2; discussed in Ch. 24).

Antibiotic or steroid-induced stomatitis

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

Acute oral candidiasis may complicate corticosteroid or antibiotic therapy, particularly with long-term, broad-spectrum antimicrobials, such as tetracycline.

Clinical features

There is widespread erythema and soreness of the oral mucosa, sometimes, with thrush.

Diagnosis

This is a clinical diagnosis, but if the aetiology is not absolutely clear a blood picture and smears for fungal hyphae and culture may be helpful management.

Management

- The causal drug should be stopped if possible.
- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs and, therefore, an azole is preferred. Some cases respond only to systemic fluconazole or itraconazole.

Median rhomboid glossitis

Median rhomboid glossitis (MRG), or glossal central papillary atrophy, is a depapillated rhomboidal area in the centre line of the dorsum of the tongue, just anterior to the sulcus terminalis (Fig. 23.4)

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

Candida species colonize mainly the posterior dorsum of the tongue, even in healthy patients, but MRG is predisposed by:

- smoking
- denture wearing
- corticosteroid sprays/inhalers
- HIV infection.

Aetiology and pathogenesis

Formerly thought to be caused by persistence of the tuberculum impar, this lesion is now thought to be related to candidiasis because:

- culture frequently shows *Candida*, although often in a mixed bacterial/fungal microflora
- histopathologically, candidal hyphae infiltrate the superficial layers of the parakeratotic epithelium and a PMNL infiltrate occupies the epithelium, with elongated hyperplastic rete ridges (pseudoepitheliomatous hyperplasia), and a lymphocyte infiltration in the corium. Thus, there can be a trap for the unwary, since the lesion may be mistaken for a cancer (Fig. 23.5).

Clinical features

MRG is only rarely sore, but is more usually detected incidentally by the patient or dentist. It is characterized by:

- an area of papillary atrophy, which is usually reddish or red and white, or occasionally white. It is elliptical or



Fig. 23.4 Median rhomboid glossitis

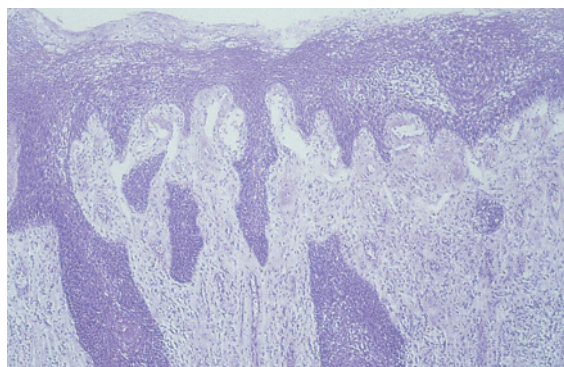


Fig. 23.5 Median rhomboid glossitis, showing histopathological appearance that has led to confusion with carcinoma

rhomboidal in shape, symmetrically placed centrally at the midline of the tongue, just anterior to the circumvallate papillae (see Fig. 23.4).

- Occasionally by a hyperplastic, or even lobulated exophytic appearance.

Diagnosis

MRG is usually a clinical diagnosis. Biopsy is rarely indicated; histology shows irregular epithelial hyperplasia, which resembles, but is not, a carcinoma (because of the pseudoepitheliomatous hyperplasia) (Fig. 23.5).

Rarely, is there a need for blood picture, smears for fungal hyphae or culture.

Management

- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs, and some cases respond only to systemic fluconazole.

Erythematous candidiasis in HIV disease

Incidence

It is uncommon.

Age

It can occur at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Predisposing factors

- The immunological defect.
- Smoking.
- Corticosteroid therapy.
- Broad-spectrum antibiotic therapy.
- Xerostomia (from HIV-salivary gland disease, or some antiretroviral agents which also have this effect).

Clinical features

- The clinical presentation is of irregular erythematous macules and/or patches, generally on the dorsum of the tongue, palate or buccal mucosa.
- Lesions are often seen in the central palate and sometimes termed 'thumbprint lesions' (Fig. 23.6)
- Lesions on the dorsum of the tongue present as glossitis or depapillated areas.
- There can be an associated angular stomatitis.

Diagnosis

This is a clinical diagnosis; biopsy is only rarely indicated. Occasionally there is a need for smears or culture.

Management

- Tobacco habits should be stopped.
- Antiretroviral treatment.



Fig. 23.6 Erythematous candidiasis in HIV disease



Fig. 23.7 Multifocal candidiasis

- Since the lesions in HIV disease may prove poorly responsive to the polyene antifungal drugs, systemic fluconazole is usually indicated.

Chronic multifocal oral candidiasis

In a minority of apparently healthy individuals, chronic candidal infection may be seen in multiple oral sites, and this is termed 'chronic multifocal oral candidiasis' (Fig. 23.7). Diagnostic criteria include:

- lesions of more than 1 month duration
- an absence of predisposing medical conditions.

It excludes patients who have received radiotherapy or drugs of the following types: antibiotics, anti-inflammatory or immunosuppressive drugs, cytotoxic or psychotropic agents.

Incidence

It is uncommon.

Age

Adults usually; most of the patients are in their fifth or sixth decade.

Sex

Most patients are males.

Geographic

No known geographical incidence.

Predisposing factors

Tobacco smoking is a known risk factor.

Clinical features

Various combinations can be seen, including:

- retrocommissural leukoplakia, which is the most constant component
- angular stomatitis, which is unilateral or bilateral and encountered mainly in denture-wearers
- median rhomboid glossitis
- palatal red irregular patches.

Diagnosis

This is a clinical diagnosis. A blood picture, smears for fungal hyphae and culture may help management.

Management

- Tobacco habits should be stopped.
- Antifungals are indicated. However, the lesions may prove poorly responsive to the polyene antifungal drugs and some cases respond only to systemic fluconazole.

Websites

<http://www.emedicine.com/emerg/topic76.htm>

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24

Denture-related stomatitis

Key points

- Denture-related stomatitis is a symptomless red lesion under a dental appliance.
- *Candida* and bacterial species are commonly causal.
- *Candida* proliferates in the dental plaque, dental appliance surface and on the mucosa.
- Candidiasis may also cause soreness at the commissures (angular cheilitis).
- Treatment includes correcting the local ecological factors, and improving appliance hygiene, together with antifungal medication.

Introduction

Denture-related stomatitis (denture sore mouth; chronic atrophic candidiasis) consists of mild inflammation and erythema of the mucosa beneath a denture, usually a complete upper denture.

Incidence

Common; in some studies of institutionalized elderly denture-wearing patients, figures as high as 70% have been found, but it is overall considerably less common, particularly in normal healthy subjects.

Age

This is a disease mainly of the middle-aged or elderly.

Sex

It is slightly more prevalent in women than men.

Geographic

This is seen worldwide.

Predisposing factors

- Dental appliance wearing (mainly maxillary dentures), especially when worn throughout the night, or with a dry mouth, is the major predisposing factor.
- Diabetes or a high carbohydrate diet occasionally predispose.
- HIV is a rare underlying factor.
- Factors that are usually *not* significant include:
 - allergy to the dental material (if it were, denture-related stomatitis would affect mucosae other than just that beneath the appliance)
 - trauma; the condition is more common beneath maxillary dentures than mandibular dentures, yet trauma is more common under the latter
 - pharmacological agents
 - smoking.

Aetiology and pathogenesis

- Dentures can produce a number of ecological changes, including accumulation of microbial plaque (bacteria and/or yeasts) on and in the fitting surface of the denture and the underlying mucosa. In some persons, the cause appears to be related to a non-specific plaque. This plaque undergoes sequential development, and is colonized by *Candida* organisms and, though there is no increased aspartyl proteinase production from the *Candida* involved, the decreased salivary flow and a low pH under the denture probably will result in a high *Candida* enzymatic activity, which can cause inflammation.
- Yeasts, such as *Candida*, are isolated in up to 90% of persons with denture-related stomatitis, but even 66% of denture wearers have them. When *Candida* species are involved in denture-related stomatitis, the more common terms '*Candida*-associated denture stomatitis', 'denture-induced candidiasis' or 'chronic atrophic candidiasis' are used. The most frequently isolated organism is *Candida albicans*.
- *Candida*, however, is not the only microorganism associated with denture-related stomatitis; occasionally other factors, such as bacterial infection, or mechanical irritation are at play.



Fig. 24.1 Denture-related stomatitis



Fig. 24.2 Denture-related stomatitis (denture in situ)

Table 24.1
Newton classification of denture-related stomatitis

Type	Definition	Comment
1	Localized simple inflammation or a pinpoint hyperaemia	Early lesion usually
2	Erythematous or generalized simple type presenting as more diffuse erythema involving a part of, or the entire, denture-covered mucosa	Common type
3	Granular type (inflammatory papillary hyperplasia) commonly involving the central part of the hard palate and the alveolar ridge	Uncommon

- Histological examination of the soft tissue beneath dentures has shown proliferative or degenerative responses with reduced keratinization and thinner epithelium.
- It not yet clear why only some denture-wearers develop denture stomatitis, since most patients with denture-related stomatitis appear otherwise healthy and they have no serious cell-mediated immune defects, but they may sometimes be deficient in migration-inhibition factor (MIF) and may have overactive suppressor T cells or other T lymphocyte or phagocyte defects.

Clinical features

The characteristic presenting features of denture-related stomatitis are:

- an absence of symptoms
- chronic erythema and oedema of the mucosa that contacts the fitting surface of the denture, usually a complete upper denture (the denture-bearing area); the mucosa below lower dentures is rarely involved (Figs 24.1 and 24.2)
- uncommon complications, which include:
 - angular stomatitis
 - papillary hyperplasia in the vault of the palate.

Classification

Denture-related stomatitis has been classified into three clinical types (Newton's types), increasing in severity (Table 24.1).

Diagnosis

- This is a clinical diagnosis.
- Diabetes should be excluded, and a blood picture, smears for fungal hyphae and culture or other investigations, such as HIV serology, may be indicated if there is angular stomatitis, or other oral or systemic lesions.

Management

- Patient information is probably the most important aspect in management.
- Any underlying systemic disease should be treated where possible.

Patient information sheet**DENTURE CARE**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- If you still have some natural teeth, these will need regular attention, because wearing a denture can encourage food accumulation.
 - Keep your dentures as clean as natural teeth. Clean both surfaces of your dentures (inside and outside) after meals and at night. Use washing-up liquid and a tooth brush and lukewarm water and hold it over a basin containing water, in case you drop the denture, which could cause it to break. Never use hot water, as it may alter the denture colour. A disclosing agent, for example Rayner's Blue or red food colouring (available at most supermarkets), can be applied with cotton buds, to help you see whether you are cleaning the denture thoroughly enough. If stains or calculus deposits are difficult to remove, try an overnight immersion (e.g. Dentalur, Milton or Steradent) or an application of Denclen.
 - Your dentures should be left out overnight, so that your mouth has a rest. It is not natural for your palate to be covered all the time, and the chances of getting an infection are increased if the dentures are worn 24 hours a day. Ensure you leave the dentures out for at least some time and keep them in water, Dentalur or Steradent, or in a damp tissue, as they may distort if allowed to dry out.
 - Special precautions for dentures with metal parts: Denclen, Dentalur and Milton may discolour metal, so use with care. Brush briefly to remove stains and deposits, rinse well with lukewarm water and do not soak overnight in these solutions.
 - Before re-use, brush the dentures to remove loosened deposits.
- The denture plaque and fitting surface is infested, usually with *Candida albicans*, which should be removed. Dentures should be left out of the mouth at night, cleaned and disinfected, and stored in an anti-septic denture cleanser. These can be divided into groups according to their main components: alkaline peroxides, alkaline hypochlorites, acids, yeast lytic enzymes, proteolytic enzymes and disinfectants, such as hypochlorite. Denture soak solutions containing benzoic acid completely eradicate *C. albicans* from the denture surface as it is taken up into the acrylic resin and eliminates the organism from the internal surface of the prosthesis. An oral rinse containing chlorhexidine gluconate also results in complete elimination of the presence of *C. albicans* on the acrylic resin surface of the denture, and in reduction of palatal inflammation. A protease-containing denture soak (alcalase protease) is also an effective way of removing denture plaque, especially when combined with brushing.

Patient information sheet**DENTURE SORE MOUTH**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- Denture sore mouth is common but not sore.
- It is caused by a fungus (*Candida*) that usually lives harmlessly in the mouth and elsewhere.
- It is caused mainly by wearing a dental appliance, which allows the fungus to grow.
- It may be precipitated by prolonged appliance-wearing, especially at night.
- It predisposes to sores at the corners of the mouth.
- It has no serious long-term consequences.
- Blood tests, microbiological studies or biopsy may be required.
- It may be controlled by:
 - leaving out the denture, to allow the mouth to heal
 - disinfecting the denture
 - using antifungal creams or gels (e.g. Daktarin) or tablets (e.g. Nystan, Fungilin, Diflucan) regularly for up to 4 weeks.
 - the dentures may require adjustment.

Hypochlorite is an effective anti-candidal, but can turn chrome cobalt dentures black.

- The mucosal infection is eradicated by brushing the palate and using antifungals for 4 weeks. Effective agents include nystatin pastilles or suspension, amphotericin lozenges or miconazole gel or fluconazole suspension or tablets, administered concurrently with an oral antiseptic such as chlorhexidine, which has antifungal activity. Miconazole lacquer or antifungals, such as fluconazole in tissue conditioners applied to the denture fitting surface, are also effective
- Studies of sensitivity to antifungal agents have shown that isolates from different strains are sensitive to amphotericin and nystatin, but less sensitive to miconazole. Fluconazole is as effective as newer agents, such as itraconazole. The cyclodextrin solution of itraconazole and capsule preparations of itraconazole are equally effective adjuncts in the treatment but, because of side-effects, capsules are preferred.

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25

Erythema migrans

Key points

- Erythema migrans is a common genetic condition, where the tongue has red patches ('geographic' tongue).
- It may cause a sore tongue.
- There is no available reliable treatment.

Introduction

Erythema migrans (geographic tongue, benign migratory glossitis) is a common cause of a sore tongue, where the tongue has red patches that resemble a map ('geographic' tongue) (Fig. 25.1). It is unrelated to erythema migrans of the skin.

Incidence

It occurs in 1–2% of adults.

Age

It may be seen at any age.

Sex

It can occur in either sex.

Geographic

It has no known geographic incidence.

Aetiology and pathogenesis

- There is a genetic background; there is:
 - often a family history
 - sometimes an HLA association (an increased incidence of HLA-Cw6, DR5 and DRW6 antigens and a decrease in B51 antigen)



Fig. 25.1 Erythema migrans (geographic tongue), showing typical lesions

- an increased incidence of HLA-B15 in atopic patients with erythema migrans.
- Patients with fissured tongue often have erythema migrans.
- Some patients have psoriasis, probably about 4% of cases. Some have a family history of psoriasis.
- Some patients have atopic allergies, such as hay fever, and a few relate the discomfort or oral lesions to various foods (e.g. cheese).
- A few patients have diabetes mellitus
- Histologically there is epithelial thinning at the centre of the lesion with an inflammatory infiltrate mainly of polymorphonuclear leukocytes (PMNL), reminiscent of psoriasis – even in patients without psoriasis (Fig. 25.2).

Clinical features

- Erythema migrans typically involves the dorsum of the tongue, sometimes the ventrum, and rarely other areas on the oral mucosa.
- There are irregular, pink or red depapillated map-like areas, which change in shape, increase in size, and spread or move to other areas, sometimes within hours (Fig. 25.3).
- The red areas are often surrounded by distinct yellowish, slightly raised margins.
- There is increased thickness of the intervening filiform papillae.
- It is often asymptomatic.
- A small minority complain of soreness and these patients are virtually invariably middle-aged. If sore,

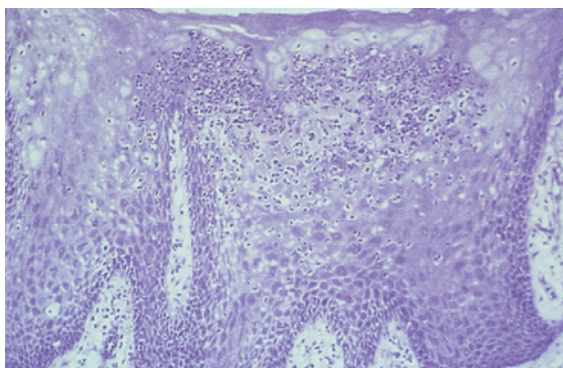


Fig. 25.2 Erythema migrans (geographic tongue), showing typical histopathological features resembling psoriasis



Fig. 25.3 Erythema migrans (geographic tongue), showing typical lesions in a fissured tongue – a common association

this may be noted especially with acidic foods (e.g. tomatoes or fruits) or cheese. Why the condition should give rise to symptoms after it has presumably been present for decades is unclear.

- Many patients with a fissured tongue (scrotal tongue) also have erythema migrans.

Diagnosis

- The diagnosis is clinical mainly from the history of a migrating pattern and the clinical appearance.
- Very similar lesions may be seen in psoriasis and Reiter syndrome (transiently).

- There also may be confusion with glossitis, lichen planus and lupus erythematosus.

Management

- Patient information is an important aspect in management.
- Blood examination may rarely be necessary to exclude anaemia if there is confusion with a depapillated tongue of glossitis.
- Reassurance remains the best advice that can be given.

Websites

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26

Erythema multiforme

Key points

- Erythema multiforme (EM) is an acute, often recurrent, hypersensitivity reaction.
- The cause of EM may remain elusive, but herpes simplex and drugs are commonly implicated.
- EM affects the mouth with serosanguinous exudates on the lips, and widespread ulceration
- Some patients develop lesions on other mucosae, or skin.
- Treatment usually involves corticosteroids.

Introduction

Erythema multiforme (EM) is an acute, often recurrent, hypersensitivity reaction affecting mucocutaneous tissues, seen especially in males, and characterized by serosanguinous exudates on the lips, mouth ulceration and sometimes lesions on other mucosae, or target-like lesions on the skin.

Incidence

It is uncommon.

Age

Younger adults (peaks between 20 and 40 years of age) are affected; 20% of cases occur in children.

Sex

It is more common in males.

Geographic

It is seen worldwide.

Predisposing factors

- There may be a genetic predisposition to EM, and HLA associations.
- HLA associations are of:
 - HLA DQ3 in patients with herpes-simplex-associated EM (HAEM)
 - HLA DQB1*0402 in patients with extensive mucosal EM
 - HLA-B15(B62), HLA-B35, HLA-A33, HLA-DR53 and HLA-DQB1*0301 in patients with recurrent EM.

Aetiology and pathogenesis

- A range of usually exogenous factors trigger what appears to be an immunologically-related reaction (Fig. 26.1) with the appearance in the epithelium of cytotoxic effector cells, mainly activated CD8⁺ T lymphocytes and macrophages, but also neutrophils and T lymphocytes which induce apoptosis of keratinocytes leading to satellite cell necrosis and thus sub- and intraepithelial vesiculation (Fig 26.2). The Fas/FasL system is significantly expressed in SJS/TEN lesions, but not in EM, where this apoptotic pathway presumably does not play a pivotal role in the epithelial damage.
- The trigger for EM is unclear in most patients.

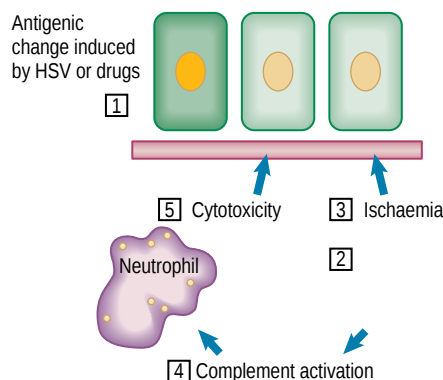


Fig. 26.1 Aetiopathogenesis of erythema multiforme

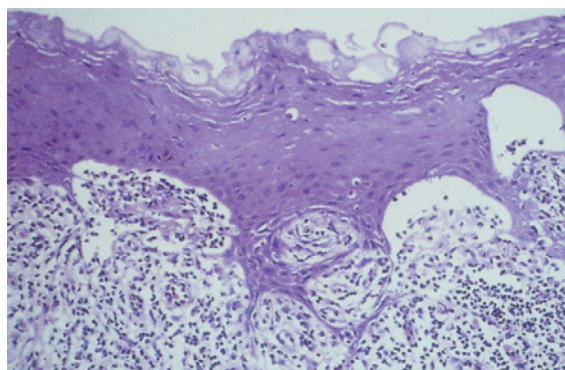


Fig. 26.2 Histopathology of erythema multiforme



Fig. 26.3 Labial swelling and crusting in erythema multiforme

- Where the trigger can be identified, it is mainly:
 - infective agents: particularly herpes simplex virus (herpes-associated EM – HAEM). HSV is implicated in 70% of recurrent EM. Numerous other organisms, particularly mycoplasmas, have also been implicated
 - drugs: such as antimicrobials (sulphonamides, e.g. co-trimoxazole), cephalosporins, aminopenicillins, quinolones, barbiturates, non-steroidal anti-inflammatory drugs, anticonvulsants, protease inhibitors and many others may trigger severe EM or, in particular, toxic epidermal necrolysis
 - immune conditions: such as BCG or hepatitis B immunization, sarcoidosis, graft-versus-host disease, inflammatory bowel disease, polyarteritis nodosa or systemic lupus erythematosus
 - food additives or chemicals: such as benzoates, nitrobenzene, perfumes, terpenes
 - erythema multiforme associated with phenytoin and cranial radiation therapy is termed EMPACT.

Clinical features

EM may present within a wide spectrum of severity, from mild limited disease (mild EM) to a severe, widespread and life-threatening illness (major EM). Most patients with EM (70%), of either minor or major forms, have oral lesions.

Oral lesions

Oral lesions:

- precede lesions on other stratified squamous epithelia, or may arise in isolation.
- typically present with:
 - diffuse and widespread macules that progress through to blisters and ulceration

- lips that become swollen and cracked, bleeding, and crusted (**Fig. 26.3**)
- lesions on the non-keratinized mucosae and most pronounced in the anterior mouth.
- Recur in about 25%. The periodicity can vary from weeks to years; usually attacks last for 10–20 days once or twice a year.
- Resolve after about 6 episodes.

Skin lesions

Skin lesions:

- commonly affect the distal extremities, especially the extensor surfaces of the arms, legs, elbows, knees, dorsum of hands and feet
- are usually macules that are symmetric, round, erythematous and slightly pruritic or non-itchy and may evolve into papules or plaques that frequently display a circumferential pallor and evolve into target or iris lesions
- are large annular (ring-shaped) target lesions with concentric rings. The well-demarcated centre of the papule forms a necrotic ulcer, which results in a depressed white, yellow or grey area surrounded by a red edge and then a pale oedematous ring; a bright red margin may surround this pale ring.

Other mucosae

Eye involvement may cause lacrimation and photophobia. Genital lesions are painful and may result in urinary retention.

Forms of EM

The degree of mucosal involvement is the distinguishing feature between minor and major forms:

- Minor erythema multiforme:
 - affects only one site: the mouth alone, or skin or other mucosae
 - rashes are various, but are typically 'iris' or 'target' lesions or bullae on the extremities.
- Major erythema multiforme [Stevens–Johnson syndrome (SJS)]:
 - begins with a prodrome in about 30% of cases, may begin within 1–3 weeks of starting a new drug, lasts 1–2 weeks before the onset of the mucocutaneous manifestations, and presents with flu-like symptoms, sore throat, headache, arthralgias, myalgias or fever
 - almost invariably involves the oral mucosa
 - causes widespread lesions also affecting the skin, eyes, genitals, pharynx, larynx and oesophagus. May present with bullous and other rashes, pneumonia, arthritis, nephritis or myocarditis. Ocular changes that resemble those of mucous membrane pemphigoid (dry eyes and symblepharon) may result. Balanitis, urethritis and vulval ulcers may occur
 - may present with pneumonia, arthritis, nephritis or myocarditis.
- *HSV-induced EM major* is characterized by mucosal erosions plus typical or raised atypical targets and epidermal detachment involving less than 10% of the body surface and usually located on the extremities and/or the face.
- *Drug-induced SJS* is characterized by mucosal erosions plus widespread distribution of flat atypical targets or purpuric macules and epithelial detachment involving less than 10% of body surface on the trunk, face and extremities.

Diagnosis

A diagnosis of erythema multiforme can be difficult to readily establish, and there can be a need to differentiate from viral stomatitides, pemphigus, toxic epidermal necrolysis and the subepithelial immune blistering disorders (pemphigoid and others):

- The diagnosis is mainly clinical; the Nikolsky sign is negative.
- It may be helpful to undertake serology for HSV or *Mycoplasma pneumoniae*, or for other micro-organisms.
- Biopsy of perilesional tissue, with histological and immunostaining examination, are essential if a specific diagnosis is required. Biopsy shows:
 - intraepithelial oedema and spongiosis early on
 - satellite cell necrosis (individual eosinophilic necrotic keratinocytes surrounded by lymphocytes)
 - sub- or intraepithelial vesiculation
 - intense lymphocytic infiltration
 - immune deposits; fibrin and C3 at the basement membrane zone
 - vacuolar degeneration of the junctional zone and severe papillary oedema
 - increased vascularity
 - perivascular lymphocytic infiltrate (CD4⁺ more than CD8⁺ T lymphocytes) with a few neutrophils and occasional eosinophils
 - perivascular IgM, C3 and fibrin
 - keratinocyte necrosis and dermal inflammation containing eosinophils may occur in drug-related cases.
- However, pathology can be variable and immunostaining is not specific.
- In EM major, a complete blood count, urea and electrolytes, erythrocyte sedimentation rate, liver function tests, and cultures from blood, sputum and erosive areas should be taken.

Management

Spontaneous healing can be slow – up to 3 weeks in minor EM and up to 6 weeks in EM major:

- No specific treatment is available, but supportive care is important; a liquid diet and intravenous fluid therapy may be necessary in EM major, and electrolytes and nutritional support should be started as soon as possible.
- Patient information is an important aspect in management.
- Early ophthalmologic and dermatological consultation are needed.
- Precipitating factors, when identified, should be treated.
- Oral hygiene should be improved with 0.2% aqueous chlorhexidine mouthbaths.
- Antimicrobials may be indicated:
 - Aciclovir or valacyclovir in EM related to herpes simplex virus
 - Tetracycline in EM related to *Mycoplasma pneumoniae*.
- The use of corticosteroids is controversial but:
 - minor EM may respond to topical corticosteroids, though systemic corticosteroids may still be required
 - major EM should be treated with systemic corticosteroids (prednisolone) and/or azathioprine or other immunomodulatory drugs. Levamisole, dapsone, ciclosporin and thalidomide have occasionally been used to some effect. Plasmapheresis or intravenous immunoglobulins possibly have a place in the management of severe disease.
- patients with major EM, such as the Stevens–Johnson syndrome, may need to be admitted for hospital care.

Prophylactic care

- Avoid triggers.
- Adequate hydration and nutritional support.

Websites

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27

Erythroplakia, leukoplakia, keratosis and other potentially malignant lesions

Key points

- Potentially malignant (sometimes termed *premalignant*) clinically obvious lesions include actinic cheilitis, erythroplakia (erythroplasia – red patch), and leukoplakia (white patch).
- Risk factors may include tobacco use, alcohol use, betel nut chewing and sunlight exposure.
- Diagnosis and prognosis are aided by biopsy.
- Factors predictive of future malignant transformation may include dysplasia, history of cancer in the upper aerodigestive tract, expression of P53 tumour suppressor protein, and changes involving chromosomes 3p or 9p.
- Treatment involves removing risk factors, and excision of dysplastic lesions.

Introduction

Most mouth carcinomas appear to arise in apparently normal mucosa, but some are preceded by potentially malignant (sometimes termed *premalignant*) clinically obvious lesions. These include:

- actinic cheilitis (Ch. 42)
- erythroplakia (erythroplasia – red patch) – defined by the World Health Organization as ‘any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterized clinically or pathologically as any other recognisable condition’. This has a very high malignant potential (Fig. 27.1).
- leukoplakia (white patch) – defined by the World Health Organization as ‘clinical white patches that cannot be wiped off the mucosa and cannot be classified clinically or microscopically as another specific disease entity (such as lichen planus)’. Leukoplakia is, thus, a clinical diagnosis only and can only be made by exclusion. This can have a malignant potential. In some types the malignant potential is high, particularly in:
 - speckled leukoplakia (red and white patch) (Fig. 27.2)



Fig. 27.1 Erythroplakia: usually a potentially malignant lesion. Carcinoma developed in this patient, who actually had long-standing lichen planus with lichenoid dysplasia.

- verrucous leukoplakia.

Conditions that may predispose to malignancy include:

- lichenoid lesions; cases of dysplasia with a lichenoid appearance (lichenoid dysplasia)
- discoid lupus erythematosus
- submucous fibrosis
- previous oral malignancy
- immunosuppression
- syphilitic glossitis
- dyskeratosis congenita
- Paterson-Kelly syndrome (sideropenic dysphagia; Plummer-Vinson syndrome).

Although some clinically potentially malignant lesions may show no dysplasia on biopsy examination (Fig. 27.3), most show dysplasia, and this appears to be the most predictive marker in current use for



Fig. 27.2 Speckled leukoplakia: often a potentially malignant lesion

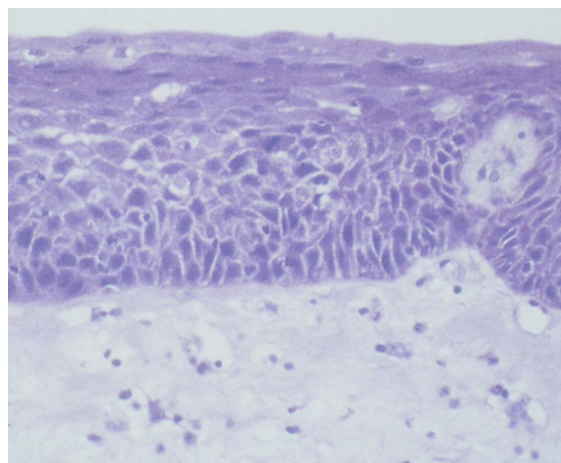


Fig. 27.4 Dysplasia: moderate

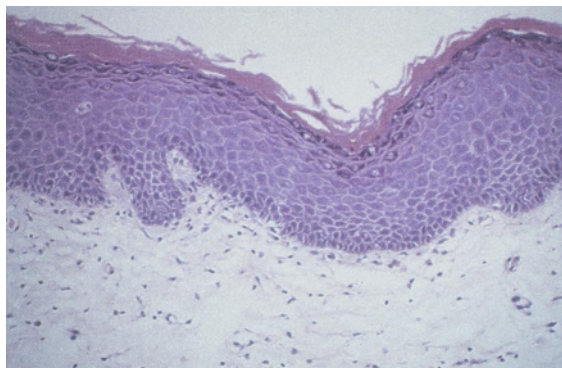


Fig. 27.3 Leukoplakia: no dysplasia detectable from this biopsy

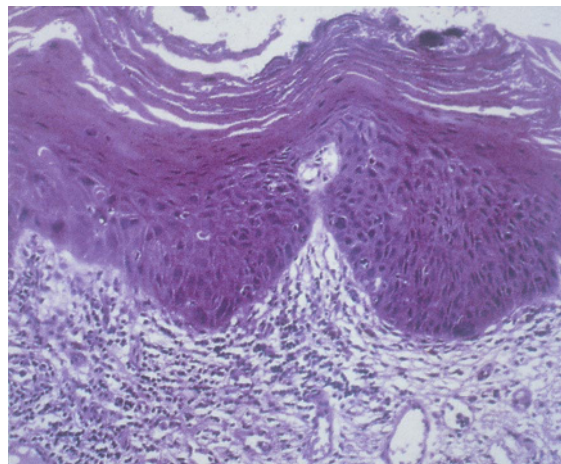


Fig. 27.5 Dysplasia: severe, and suggestive of a potentially malignant lesion

malignant potential. *Cellular atypia* is the main feature – discussed in Chapter 22. Features of dysplasia are, in general:

- *mild to moderate dysplasia* is the term used where few of the features of dysplasia are present and the epithelium is reasonably well organized (Fig. 27.4)
- *severe dysplasia* is the term used if organization is disrupted and many cellular abnormalities present (Fig. 27.5), but the epithelial basement membrane is not breached.

Factors predictive of future malignant transformation may also include:

- history of cancer in the upper aerodigestive tract
- expression of P53 tumour suppressor protein
- changes involving chromosomes 3p or 9p; these are termed 'loss of heterozygosity,' or LOH
- chromosomal polysomy (as shown in Table 27.1).

Table 27.1
Potentially malignant lesions: chromosomal polyploidy and prognosis

DNA content	% transformation in 10 years
Diploid	3
Tetraploid	60
Aneuploid	84

Habits that may predispose to potential malignancy include:

- tobacco use (Fig. 27.6)
- alcohol use
- betel nut chewing (Figs 27.7 and 27.8)
- sunlight exposure.



Fig. 27.6 Leukoplakia in a person who for most of his adult life drank a bottle of vodka and smoked 20 cigarettes daily



Fig. 27.7 Betel chewing in a Bangladeshi person who developed keratosis in the buccal mucosa



Fig. 27.8 Betel-induced leukoplakia

Actinic cheilitis

Incidence

Actinic cheilitis (actinic keratosis of lip, solar keratosis, solar cheilosis) is common in chronically sun-exposed individuals.

Age

Occurs mainly in adults.

Sex

Most prevalent in men.

Geographic

Mainly seen in persons from the tropics and less in black people.

Predisposing factors

Sun damage is most common in:

- hot, dry regions
- outdoor workers
- fair-skinned people.

Clinical features

Actinic cheilitis is a chronic premalignant keratosis of the lip caused by long exposure to solar irradiation. Most is therefore seen:

- on the lower lip, with sparing of the oral commissures
- in fair-skinned men
- in the fourth to eighth decade of life
- particularly in those who have had prolonged exposure to sunlight (e.g. fishermen, skiers, windsurfers, sailors).

In the early stages there may be redness and oedema, but later the lip becomes dry and scaly and wrinkled with grey to white changes in pigmentation. Lesions may appear as a smooth or scaly, friable patch or can involve the entire lip. Later, the epithelium becomes palpably thickened with small greyish white plaques. Eventually, warty nodules may form, which may evolve into squamous cell carcinoma.

Diagnosis

A careful history and a biopsy are often indicated.

Management

Prevention is advised, especially in high-risk individuals. Particular care to protect the vermilion of the lips with adequate sunscreens is needed in patients with

photosensitivity disorders, and in those whose exposure to ultraviolet light (especially UVB) is high, such as mountaineers and skiers.

Management of established actinic cheilitis is required both to relieve symptoms and to prevent development of squamous cell carcinoma. This is best achieved by the removal of the premalignant epithelium by topical chemoexfoliants and surgery.

Following management, prevention of recurrence by the regular use of a UVA and UVB protective sunscreen is advisable.

Erythroplakia (erythroplasia)

Erythroplastic lesions are well-defined velvety red plaques that are usually (at least 85%) severely dysplastic or frankly malignant. Erythroplasia is the oral lesion with the most severe dysplasia and greatest predilection to develop to carcinoma.

Incidence

Rare: mainly seen in elderly men. It is much less common than leukoplakia.

Age

Occurs in the middle aged and the elderly.

Sex

Occurs mostly in men.

Geographic

It has no known geographic incidence.

Predisposing factors

Unknown, but tobacco and alcohol use are probably involved.

Aetiology and pathogenesis

Erythroplasia contains areas of dysplasia, carcinoma *in situ*, or invasive carcinoma in virtually every case. Carcinomas are seen 17 times more frequently in erythroplakia than in leukoplakia, and these are therefore the most potentially malignant of all oral mucosal lesions, but erythroplasia is far less common than leukoplakia.

Clinical features

Red velvety patch of variable configuration, usually level with or depressed below surrounding mucosa, commonly on:

- soft palate
- floor of mouth
- buccal mucosa (Fig. 27.9).

Some erythroplakias are associated with white patches, and are then termed speckled leukoplakia (Box 27.1).



Fig. 27.9 Erythroplakia: usually a potentially malignant lesion

► Box 27.1

Classification of leukoplakias and erythroplakia

Leukoplakia: homogeneous

- Flat
- Corrugated
- Pumice-like
- Wrinkled

Leukoplakia: non-homogeneous

- Verrucous
- Proliferative and verrucous
- Nodular
- Erythroleukoplakia (speckled)

Erythroplakia

- Uniformly red
- Red with white nodules

After Axell et al (1984)

Diagnosis

A biopsy should be done to examine for epithelial dysplasia and carcinoma and the lesion should be differentiated from inflammatory and atrophic lesions (e.g. in deficiency anaemias, geographic tongue, lichen planus).

Management

Patient information is an important aspect in management. Any causal factor, such as tobacco use should be stopped and lesions removed. There is no hard evidence as to the ideal frequency of follow-up, but it has been suggested that patients with mucosal potentially malignant lesions be re-examined:

- within 1 month
- at 3 months
- at 6 months
- at 12 months
- annually thereafter.

Leukoplakia

Leukoplakia can be totally benign or sometimes can be precancerous or a marker for cancer elsewhere in the upper aerodigestive tract.

Incidence

Occurs in about 0.1% of the population.

Age

Occurs predominantly in the middle-aged and elderly.

Sex

Occurs more in men than women.

Geographic

It has no known geographic incidence.

Predisposing factors

These are habits such as:

- tobacco use
- alcohol use

- betel use. The leaf contains allylbenzene compounds such as chavibetol, chavicol, estragole, eugenol and methyl eugenol, and is used to include in a betel quid (paan), various spices, areca nut and often tobacco and/or slaked lime.
- sanguinarine (pseudocheilerythrine) use. This is a quaternary benzophenanthridine alkaloid extracted from some plants, including Bloodroot (*Sanguinaria canadensis*), Mexican Prickly Poppy (*Argemone mexicana*), *Chelidonium majus*, and *Macleaya cordata* and used in some oral healthcare products. It is a potent suppressor of NF-B activation and induces a rapid apoptotic response by glutathione-depletion.

Clinical features

Leukoplakias vary in size: some are small and focal, others more widespread – occasionally involving very large areas of the oral mucosa – and in other patients several discrete separate areas of leukoplakia can be seen. Leukoplakia has a wide range of clinical presentations, from homogeneous white plaques, which can be faintly white or very thick and opaque, to nodular white lesions, or lesions admixed with red lesions (see [Box 27.1](#)).

Malignant potential

The malignant potential depends on the appearance, site and some aetiological factors.

Appearance

- *Homogeneous leukoplakias*: the most common type, are uniformly white plaques – common in the buccal (cheek) mucosa and usually of low malignant potential ([Fig. 27.10](#)). Sometimes lesions are widespread, suggesting there are widespread molecular changes in the mucosa ([Fig. 27.11](#)).
- *Non-homogeneous or heterogeneous leukoplakias*: nodular, verrucous and speckled leukoplakias, which consist of white patches or nodules in a red, often eroded, area of mucosa ([Fig. 27.12](#)) have a high risk of malignant transformation and, therefore, are far more serious.

Site

High risk sites for malignant transformation include the soft palate complex and ventrolateral tongue and floor of the mouth (where sublingual keratosis has a particularly high risk of malignant change – [Fig. 27.13](#)). Sublingual keratosis is more common in women than men, has a typical ‘ebbing-tide’ appearance clinically and has a high malignant potential.

Aetiological factors

- Proliferative verrucous leukoplakia is a diffuse white and/or papillary lesion seen in elderly patients, often associated with human papilloma viruses, which has



Fig. 27.10 Leukoplakia: homogeneous type – most are benign



Fig. 27.12 Leukoplakia: speckled – has a high prevalence of malignant change

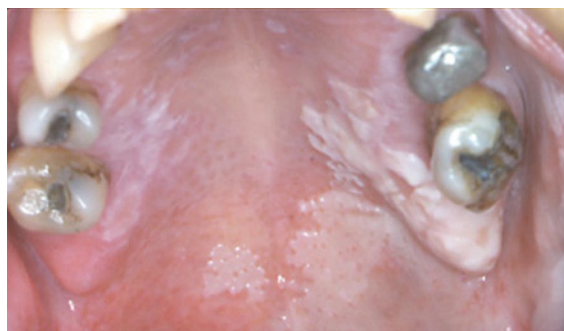


Fig. 27.11 Leukoplakia: widespread field change over, at least, the palate



Fig. 27.13 Leukoplakia: floor of mouth or sublingual type

an inexorably slow progression over one or two decades, to verrucous or squamous cell carcinoma.

- Candidal leukoplakias may be associated with an increased risk of malignant change. Chronic candidal infection is common in speckled leukoplakias and *C. albicans* can cause or colonize other keratoses, particularly in smokers, and is especially likely to form speckled leukoplakias at commissures. They may be dysplastic and have higher malignant potential than some other keratoses. Candidal leukoplakias may respond to antifungals and stopping smoking.
- Syphilitic leukoplakia, especially of the dorsum of the tongue, is a feature of tertiary syphilis rarely seen now, but the malignant potential is high.
- Hairy leukoplakia is caused by Epstein-Barr virus (EBV). It usually has a corrugated surface and affects margins of the tongue almost exclusively. It is seen in the immunocompromised and is a complication of HIV infection. It is seen in all groups at risk of HIV infection. The condition appears to be benign and self-limiting.

detect dysplasia ([Algorithm 27.1](#)). Ploidy may become useful in this respect. Biopsy is, therefore, generally indicated and is mandatory for those leukoplakias that are:

- in patients with previous or concurrent head and neck cancer
- non-homogeneous, i.e.:
 - have red areas
 - are verrucous
 - are indurated
- in a high-risk site such as the floor of the mouth or the tongue
- focal
- with symptoms
- without obvious aetiological factors.

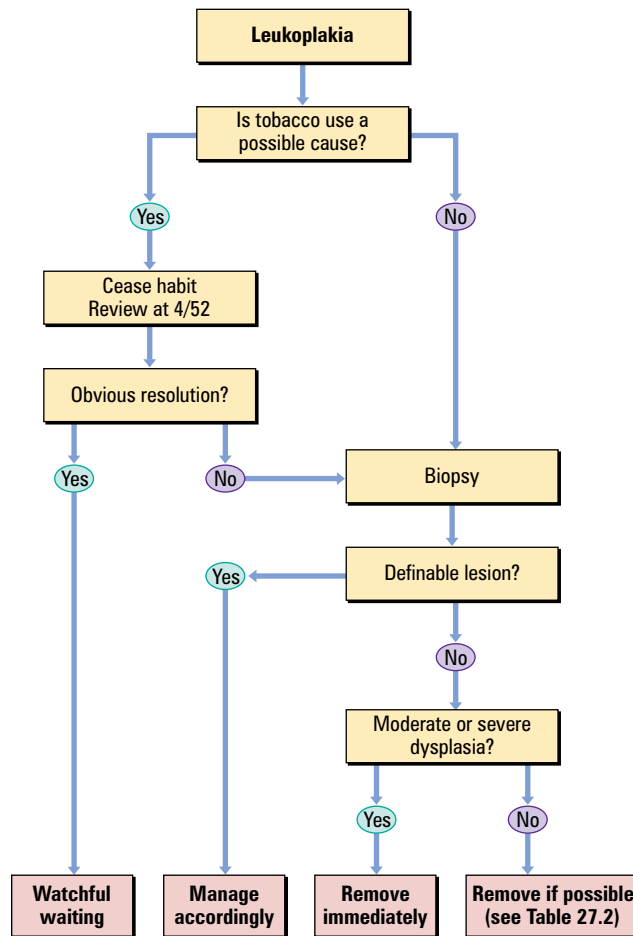
In the event of biopsy not being available, or the patient refusing scalpel biopsy, the oral brush biopsy may be helpful (see below).

Diagnosis

There are no clinical signs or symptoms that reliably predict whether a leukoplakia will undergo malignant change and, thus, there must be use of microscopy to

Identification of appropriate biopsy site

- To improve the sensitivity and specificity of lesion identification, vital tissue staining may be used, with a dye, such as toluidine (tolonium) blue. Tissue fluorescence detected by special lights may also help.



Algorithm 27.1 Management of leukoplakia

- Toluidine blue is an acidophilic metachromatic thiazine dye that selectively stains tissue acids, particularly DNA and RNA.
- The rationale for use of toluidine blue is that dysplastic cells usually contain more nucleic acid than normal cells.
- Lugol's iodine solution is also used; it produces a brown-black stain by reaction of the iodine with the glycogen, which is inversely related to the degree of keratosis. The iodine is removed by fixation in alcohol and formaldehyde during the preparation of biopsy specimens and, thus, does not interfere with the subsequent histological evaluation.
- The use of vital stains, assisted by a good measure of clinical experience, is of value in accurately diagnosing lesions. When one or both tests are positive this can assist in deciding where to perform a biopsy.
- Tissue vital stains can also help to delineate the boundaries of lesions immediately prior to surgical removal.
- Nevertheless, despite the assistance of vital staining, a negative biopsy *cannot reliably* exclude the presence of carcinoma or dysplastic foci within a lesion.

Biopsy is not always diagnostic, partly because dysplastic changes are not always demonstrable in the specimen obtained and there may be skip areas within dysplastic epithelium characterized by normal or hyperplastic epithelium. Serial sectioning of removed leukoplakic lesions may reveal a wide range of grades of dysplasia in different parts of a lesion and previously unsuspected carcinoma in up to 5%.

Features of biopsy

Leukoplakias show, to a varying degree, three main microscopic features:

- Increased keratin production: increased keratin produces the white clinical appearance of keratoses. If nuclei persist into the superficial cell layers the term 'hyperparakeratosis' is used, whereas if there is excessive mature keratin, with a prominent granular cell layer, the term 'hyperorthokeratosis' is applied. Any leukoplakia can show either or both types of change, neither of which are an index of premalignancy.

- Change in epithelial thickness: thinning (hypoplasia) or thickening (hyperplasia) may be present and, although neither are indices of premalignancy, malignant change is more likely in a hypoplastic epithelium.
- Disordered epithelial maturation: although clinical features, such as the admixture of red lesions, may suggest the degree of malignant potential of a keratotic lesion, histological assessment of the degree of disordered proliferation, maturation and organization of the epithelium (i.e. the degree of dysplasia) continues to provide the best guide. It is accepted that dysplasia may precede malignant change – the connotation of severe dysplasia being that malignant change is likely. However, some lesions that often do become malignant (such as some sublingual keratoses) do not always show a great deal of dysplasia. It is clear that only a minority of leukoplakias are preneoplastic, but the problem is to identify those which are.

Oral brush biopsy

Computer-assisted analysis of an oral brush biopsy is an aid to the oral examination that helps determine the significance of oral lesions with an epithelial abnormality. It is especially valuable for benign-appearing lesions that are easily overlooked and unrecognized, but in fact are malignant or potentially malignant.

The brush biopsy is performed without any anaesthetic and using an instrument designed to obtain a transepithelial specimen containing cells from the basal, intermediate and superficial layers. This is a crucial feature, since the basal cell layer may be the only layer of the epithelium that contains abnormal cells within a potentially malignant or malignant lesion. The laboratory evaluates every specimen for adequacy by verifying cellular representation from each layer of the epithelium, so false-negative results due to inadequate technique are minimized. The cellular morphology of the cells obtained by the brush biopsy is used to classify each brush biopsy specimen. A 'negative' result indicates that no epithelial abnormality was detected. Brush biopsy specimens displaying images of abnormal cells are classified as either 'positive' or 'atypical'. A histological section is always required to 'grade' any abnormality uncovered and thus, overall, it is recommended that scalpel biopsy should be carried out.

Identifying malignant change

Overall:

- 2–5% of all leukoplakias become malignant in 10 years
- 5–20% of leukoplakias are dysplastic

► Box 27.2

Most predictive transformation markers

- Histology
- Cancer history
- Chromosomal polysomy (ploidy)
- LOH at 3p or 9p
- p53 protein expression

- 10–35% of leukoplakias showing dysplasia proceed to carcinoma in 10 years.

Not all lesions showing dysplasia are premalignant, though many are: dysplasia may also be seen in regenerating tissue and in some infections. Histopathology and the detection of dysplasia alone clearly cannot always reliably identify early malignant changes, since it:

- is subjective; there is wide inter-examiner variability
- is subject to considerable intra-examiner variability; studies have shown pathologists to disagree with their previous diagnosis in up to 50% of cases
- samples only a small area and, thus, absence of dysplasia in a biopsy specimen does not necessarily mean that the whole lesion lacks dysplasia. Indeed, one study found carcinomas in nearly 5% of excised leukoplakias in which preoperative biopsies had not suggested dysplasia.

It is not at present possible, therefore, to reliably predict which lesions will progress to carcinoma. Over the last few years, much effort has gone into identifying the genetic changes that underlie progression to oral carcinoma. Currently, the most predictive markers of transformation to carcinoma (Box 27.2) are:

- histology
- cancer history
- chromosomal polysomy (ploidy)
- chromosomal loss of heterozygosity (LOH) at 3p or 9p
- p53 protein expression.

Conversely, while the potentially malignant nature of leukoplakias is often stressed, several studies have shown that dysplastic lesions can sometimes regress spontaneously or if risk factors are removed, with regression rates ranging from 9% to 45%.

Management

Some patients have spontaneous remission of leukoplakia, but the lesion may be potentially malignant and, thus, both behaviour (lifestyle) modification and active treatment of the lesion are indicated. The prevalence of malignant transformation in leukoplakias ranges from 2% to 35% over 10 years and is highest in lesions with severe dysplasia:

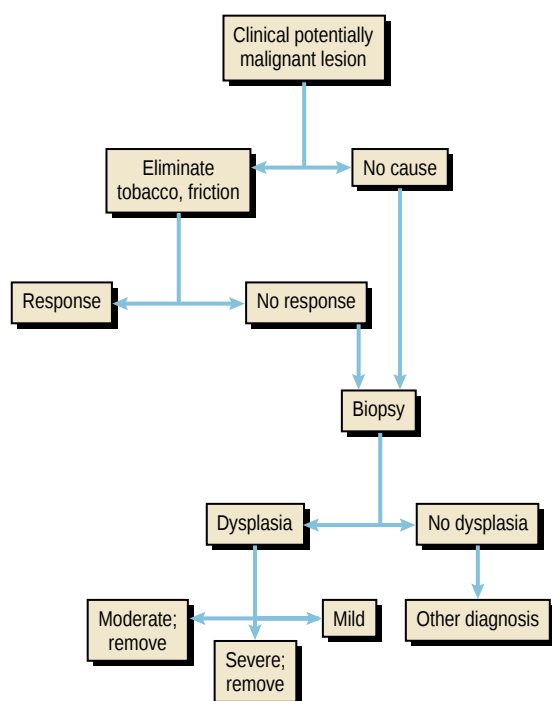


Fig. 27.14 Management of potentially malignant lesions

- Patient information is an important aspect in management.
- Removal of known risk factors (tobacco, alcohol, betel and trauma) is a mandatory first step. Up to 60% of leukoplakias regress or totally disappear if tobacco use is stopped. Leukoplakias induced by smokeless tobacco may resolve if the habit is stopped. Success is difficult to achieve, however: in one series of 145 patients operated on for oral leukoplakias, only 20 gave up smoking and only five stopped drinking alcohol.
- The patient should be re-examined 3 months after instituting this lifestyle change.
- If the lesion persists, it should be removed (Fig. 27.14). However, many patients with leukoplakias belong to lower socioeconomic groups and do not always accept or understand the need to re-attend. Therefore, many suggest removing the lesion at an earlier stage.

Medical therapies

- Up to 30% of leukoplakias can markedly improve or even resolve when aetiological factors are removed and medical therapies (anti-inflammatory and antimycotic therapy) used. Some candidal leukoplakias respond at least partially to antifungal drugs (smoking should also be stopped) and dysplasia may regress.
- Topical anticancer drugs or retinoids can cause regression and are generally well tolerated and effective, but their efficacy is only temporary, and perhaps

Patient information sheet

KERATOSIS (LEUKOPLAKIA)

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon condition.
- Sometimes it is caused by friction or tobacco.
- It is not inherited.
- It is not known to be infectious.
- In a very small number, and after years, it may lead to a tumour. You should get yourself checked regularly.
- Blood tests and biopsy may be required.
- There is no universally agreed management and this can be by simple observation, drugs or surgery. You should avoid alcohol or tobacco in future.

their best indication is when the location or extent of the lesion render surgical removal difficult. Topical treatment of leukoplakia with podophyllin solution or bleomycin has induced some regression or even total resolution of dysplasia and clinical lesions, and lesions recur more slowly than after surgery. Treatment with photodynamic therapy, in which a light-sensitizing dye is given to the patients, and light shone on the lesion to activate the dye and cause necrosis of the pathological tissue, is still in its infancy.

- Since leukoplakias are only potentially cancerous, it is generally accepted that radiotherapy or systemic chemotherapy are inappropriate treatments.

Surgery

- Surgery is an obvious option for the management of leukoplakia, certainly for patients with high predisposition to malignant transformation, such as leukoplakias that are:
 - speckled
 - verrucous
 - from high-risk sites, including the floor of the mouth/ventrum of the tongue, or soft palate/faucis
 - in a patient with previous cancer in the upper aerodigestive tract
 - dysplastic
 - polysomic (aneuploidy or tetraploidy)
 - tested positive for genetic markers, such as mutated tumour suppressor factor p53, or loss of heterozygosity on chromosomes 3p or 9p.
- 'Watchful waiting' and excision only when signs of cancerization arise appears unacceptable since even excised leukoplakias that show only dysplasia on prior biopsy may still contain carcinomatous foci. In one series of removed leukoplakias, 5–10% of lesions were found to be malignant on removal, although they had been judged both clinically to be benign and on preoperative biopsy were negative for malignancy. Even when surgical specimens of excised leukoplakias

showed only orthokeratosis, or parakeratosis with epithelial hyperplasia (no dysplasia) and minimal inflammation, some 5% of such patients subsequently developed oral squamous cell carcinoma.

- Resection with a scalpel or laser is probably the most effective and safe means of removing pathologic tissue since – unlike the case with cryosurgery, coagulation or laser vaporization – a specimen for pathologic evaluation (of histology and margins) is produced, and the pain and postoperative scarring are less with these techniques than with coagulation. Finally, laser excision (usually with the carbon dioxide laser) seems to have advantage over the use of a scalpel, as intraoperative bleeding and the need for mucosal or dermoepidermal flaps are reduced.
- Follow-up – patients should be regularly checked at 3, 6, and 12 months, and then annually for any:
 - size change
 - appearance of red lesions
 - ulceration
 - recurrences
 - new lesions.

Chemoprevention

Two different approaches have been proposed for clinical chemoprevention trials:

- Chemoprevention by treatment of oral leukoplakias to prevent malignant transformation. 13-*cis*-Retinoic acid can result in lesions regressing, but side-effects are severe and many patients do not complete the planned treatment. Moreover, lesions recur a few months after the end of the intervention. However, it is now possible to treat 'condemned at risk mucosa', though reversal of leukoplakia has not been proved to reduce the risk of developing cancer.
- Chemoprevention in patients following removal of leukoplakias. Fenretinide used in patients with negative histology for cancer following laser excision of leukoplakias is well tolerated and the preliminary

results show a significant protective effect. Unfortunately, the drug is not readily available.

In summary, chemoprevention with retinoids is not a definitive treatment because:

- after the treatment has stopped, lesions recur in a large number of cases
- adverse effects are common
- most retinoids are teratogenic.

Summary

No clinical or histological characteristics are able to reliably predict potential malignancy in leukoplakias; neither have reliable biological markers of premalignancy yet been identified. The evidence would suggest, however, that lesions with severe dysplasia are the most likely to transform; studies suggest up to 30% of these will progress to malignancy. Thus, a useful initial approach to the management of oral leukoplakias is the removal of aetiological factors coupled with simultaneous antimycotic therapy. If this does not produce results within a few weeks, surgical excision of persistent dysplastic oral leukoplakias, preferably laser resection, seems to be the most rational next step (Table 27.2). Therefore:

- treat predisposing factors
- stop habits such as use of tobacco, betel or alcohol
- surgically remove discrete lesions and those with moderate or severe dysplasia.

Keratoses

Increased keratin (hyperkeratosis or keratosis), can produce a clinical white lesion in the mouth. Microscopically, there is:

- simple orthokeratosis

Table 27.2
Minimal treatment for leukoplakias

Location	No dysplasia	Mild dysplasia	Moderate or severe dysplasia
Buccal	Watchful waiting	Watchful waiting or remove	Remove
Hard palate	Watchful waiting	Watchful waiting or remove	Remove
Dorsum of tongue	Watchful waiting	Watchful waiting or remove	Remove
Ventrum of tongue/floor of mouth	Watchful waiting	Remove	Remove
Lateral border of tongue	Watchful waiting	Remove	Remove
Fauces	Watchful waiting	Remove	Remove
Vermilion	Watchful waiting	Remove	Remove

- parakeratosis with epithelial hyperplasia and minimal inflammation
- hyperkeratosis with varying degrees of dysplasia.

Keratosis can arise from a number of aetiological factors, such as:

- friction
- tobacco or betel habits
- exposure to ultraviolet sun irradiation.

Many white lesions were formerly known as 'leukoplakia', a term causing misunderstanding and confusion. The World Health Organization defined leukoplakia as a 'white patch or plaque that cannot be characterized clinically or pathologically as any other disease'; therefore, specifically excluding defined clinicopathological entities, such as lichen planus, candidiasis and white sponge naevus, but still incorporating white lesions caused by friction or other trauma, and offering no comment on the presence of dysplasia. A subsequent International Seminar defined leukoplakia more precisely as 'a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and which is not associated with any physical or chemical causative agent except the use of tobacco'. Thus, frictional keratosis and specific tobacco-induced lesions, such as smoker's keratosis, are now termed 'keratoses' (not 'leukoplakias').

Tobacco habits

Tobacco chewing

Tobacco is chewed in many parts of the world and may induce keratosis. In many communities from the developing world, tobacco is a component of the betel quid, along with areca nut and betel leaf, and sometimes slaked lime and spices. Sometimes betel is used without tobacco (pan or paan), though others use paan with tobacco. Consumption of tobacco products has long been causally connected with oral cancer. In most industrialized countries, prevalence of smoking is higher in lower than in higher social class groups. In the USA, 40 years ago smoking prevalence in whites and blacks was about equal, but more recently blacks appear more likely to use tobacco. In the UK, this same pattern of high levels of smoking in minority ethnic groups has also been observed. This pattern of smoking is often reversed in non-industrialized countries.

Smokeless (chewing) tobacco use is also an important factor for South Asian populations in Asia and in countries such as the UK and USA. The areca (betel) nut habit, with or without tobacco use, can cause cytogenetic changes in oral epithelium and is important in the development of oral submucous fibrosis and of mouth cancer. Some chew the nut only and others prefer 'paan', which includes tobacco, and sometimes lime and catechu.

Studies from India have confirmed the association between 'paan' tobacco chewing and oral cancer, particularly cancer of the buccal and labial mucosa. In South Asian communities in the UK, most adults use tobacco and many chew betel (areca nut). Bangladeshis are particularly likely to retain the habit of betel use, and significantly more women chew and add tobacco to their quid.

Worldwide, around 20% of the population use betel quid. Malignant change is possible.

Reverse smoking (bidi)

In some communities, especially in Asia, cigarettes are smoked with the lit end within the mouth. Palatal or other oral carcinoma can result.

Pipe smoking

Diffuse whiteness over the palate is termed 'smoker's keratosis' or 'stomatitis nicotina'. The palatal minor salivary gland orifices appear red against this white background. Malignant change is uncommon.

Cigar smoking

Cigar smokers may develop stomatitis nicotina and nicotine-stained teeth. Malignant change is uncommon.

Detection of cancer and potentially malignant lesions

Unfortunately, many of the population – especially those at highest risk, such as elderly men who smoke and drink – do not seek regular dental care. Patients often present late to physicians and with advanced tumours, and treatment is then usually more mutilating, with higher morbidity and costs, and a worse prognosis. Furthermore, physicians and surgeons have often received little or no training in the examination of the mouth.

Clinicians should be aware that single ulcers, lumps, red patches or white patches, particularly if any of these are persisting for more than 3 weeks, may also be manifestations of frank malignancy: biopsy is invariably indicated. Even common, benign-looking oral lesions attributed to friction or trauma require evaluation when they persist. It should be noted that clinically differentiating potentially malignant and malignant oral lesions from those that are benign, even by highly trained professionals, is a difficult task. This is because these lesions do not often display well-defined clinical features that facilitate their recognition. Not uncommonly, potentially malignant and malignant oral lesions are asymptomatic, appear innocuous and are easily overlooked. Yet fewer than 27% of all leukoplakias, the most

common potentially malignant lesions, are ever subjected to biopsy. As a result, many are left to progress to more advanced stages or cancer.

Tobacco-induced keratoses

Tobacco is a common cause of keratosis. Men especially are affected. Tobacco use is one of the major risk factors for oral carcinoma and, if smoked, also predisposes to cancers elsewhere in the upper aerodigestive tract, bladder and other sites. Tobacco use should thus be discouraged; nicotine patches or the drug Zyban (bupropion) or Champix (varenicline) may help users break the habit.

Cigarette-induced keratosis

Mild keratosis may be seen especially on the palate, lip (occasionally nicotine stained) and at the commissures, along with nicotine-stained teeth. Malignant change is rare.

Stomatitis nicotina

Definition

Stomatitis nicotina – known as smoker's palate, smoker's keratosis, nicotinic stomatitis, stomatitis palatini, leukokeratosis nicotina palati – is a diffuse white lesion covering most of the hard palate, typically related to pipe or cigar smoking.

Incidence

It is uncommon.

Age

It occurs in middle-aged or elderly adults.

Sex

It occurs in more men than women.

Geographic

It is seen worldwide.

Predisposing factors

Smoker's keratosis is seen usually among heavy, long-term pipe smokers and some cigar smokers or reverse cigarette smoking, rarely in cigarette smokers.

Aetiology and pathogenesis

Presumably the hyperkeratosis is related to tobacco products and/or heat.

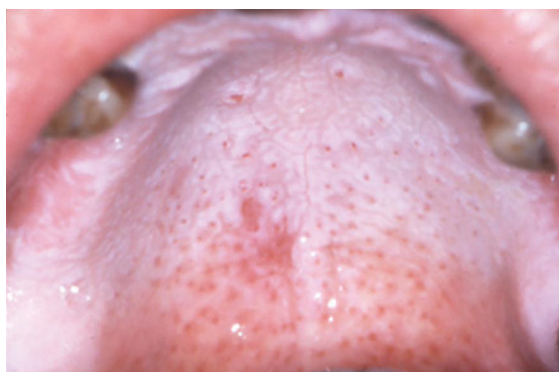


Fig. 27.15 Stomatitis nicotina

Clinical features

The appearances of smoker's keratosis are distinctive in that the palate is affected, but any part protected by a denture is spared. The teeth are often stained from the tobacco exposure. The lesion has two components, namely:

- white thickening of the palatal mucosa due to hyperkeratosis (Fig. 27.15)
- inflammatory swelling of minor mucous glands, which show as red spots against the white hyperkeratosis, as small umbilicated swellings with red centres.

Diagnosis

The clinical appearances and history are so distinctive that biopsy should not normally be necessary. The condition is not known to be potentially malignant, but the patient may develop premalignant changes at other sites in the upper aerodigestive tract.

Management

Patient information is an important aspect in management. Few patients have spontaneous remission and the patient should be encouraged to stop the causative habit.

Snuff-dippers' keratosis and other smokeless tobacco lesions

Snuff may produce keratosis, white hyperkeratotic lesions caused by snuff-dipping (holding flavoured tobacco powder in the oral sulcus or vestibule), together with gingival recession at the site of use, often the buccal sulcus. Malignant change is rare.

Incidence

It is uncommon.

Age

It occurs in adults.

Sex

It occurs equally in men and women.

Geographic

May be more common in North America and Scandinavia.

Predisposing factors

The risk factors are tobacco-chewing or snuff-dipping.

Aetiology and pathogenesis

Tobacco-chewing or snuff-dipping (holding flavoured tobacco powder in the oral sulcus or vestibule) causes white hyperkeratotic lesions in up to 20% of users. Oral snuff appears to cause more severe clinical changes than does tobacco-chewing, but dysplasia is more likely in tobacco chewers. Snuff-dipping is associated predominantly with verrucous keratoses, which can progress to verrucous carcinoma, occasionally, but only after several decades of use.

Clinical features

There is typically a white lesion in the buccal sulcus, and a high proportion of the tumours are seen in the buccal mucosa/vestibule.

Diagnosis

The diagnosis is usually obvious from the habit.

Management

Patient information is an important aspect in management. Few patients have spontaneous remission and, thus, habit cessation is indicated. Snuff dippers' lesions will resolve on stopping the habit even after 25 years of use. There is no hard evidence as to the ideal frequency of follow-up, but it has been suggested that patients with mucosal potentially malignant lesions be re-examined:

- within 1 month
- at 3 months
- at 6 months
- at 12 months
- annually thereafter.

Frictional keratosis

White lesions caused by repeated trauma, such as from the teeth or dental appliances.

Incidence

It is common.

Age

It occurs in the middle-aged and elderly.

Sex

It occurs in more men than women.

Geographic

It is seen worldwide.

Predisposing factors

Repeated trauma such as from the teeth or dental appliances.

Aetiology and pathogenesis

- Cheek biting (*morsicatio buccarum*) and horizontal white lines in the buccal mucosa at the occlusal lines (*linea alba*), and occasionally on the lateral tongue, are common and are most prevalent in anxious women, especially those with other psychologically related disorders.
- Frictional keratosis is caused by prolonged mild abrasion by such irritants as a sharp tooth, dentures or other appliances, mastication or cheek-biting. It is not uncommonly seen on edentulous ridges, especially in the partially dentate, and then presumably caused by the friction from mastication (Fig. 27.16).
- Rarely, self-mutilation is seen in psychiatric disorders, learning disability or some rare syndromes, e.g. Lesch-Nyhan syndrome and familial dysautonomia (Riley-Day syndrome).

Clinical features

Habitual cheek biting causes red and white lesions with a rough surface, invariably restricted to the lower labial and/or buccal mucosa near the occlusal line, often



Fig. 27.16 Frictional keratosis on the alveolar ridge

bilateral, but sometimes just in one area around a commissure. In the early stages, the patches are pale and translucent, but later become dense and white, sometimes with a rough surface. Occlusal lines are usually bilateral.

Diagnosis

The diagnosis is clinical and, apart from removing irritants and ceasing habits, no active treatment is required.

Management

Patient information is an important aspect in management. Frictional keratosis is completely benign, and does not require treatment. There is no evidence that continued minor trauma alone has any carcinogenic potential, but, if the patient is causing the lesion from some habit, that should be stopped.

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28 Fordyce spots

Key points

- Fordyce spots are ectopic sebaceous glands
- They are common in the lip vermillion and inside the commissures.
- No treatment is indicated.

Introduction

Fordyce spots, also known as Fordyce granules, are sebaceous glands containing neutral lipids similar to those found in skin sebaceous glands, but they are not associated with hair follicles.

Incidence

Fordyce spots are common; probably 80% of the population have them.

Age

They can occur at any age, but noticeable mainly in adults.

Sex

They can occur in either sex, but are more prominent in men.

Geographic

No known geographic incidence.

Predisposing factors

No known predisposing factors.

Aetiology and pathogenesis

Fordyce spots seem to be more obvious:

- in patients with greasy skin
- with advancing age
- in some rheumatic disorders
- in hereditary non-polyposis colorectal cancer syndrome. The most common site is then the lower gingival and vestibular oral mucosa.

Clinical features

Fordyce spots are not usually evident in infants (though they are present histologically), appearing in children after the age of 3 years, increasing during puberty and then again in later adult life.

Fordyce spots are creamy yellowish soft granules beneath the oral mucosa, usually seen along the border between the vermillion and the oral mucosa of the upper lip (Fig. 28.1) and in the buccal mucosa particularly inside the commissures, and also in the retromolar regions and lips.

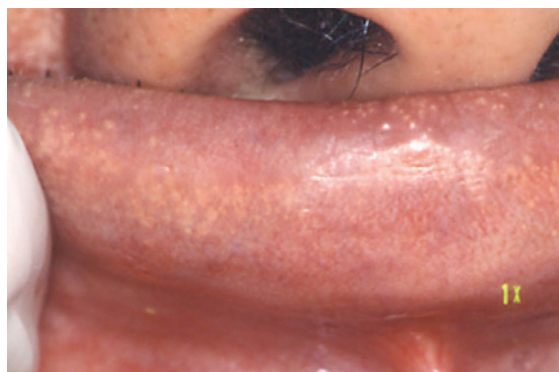


Fig. 28.1 Fordyce spots

Diagnosis and management

Fordyce spots are totally benign, though the occasional patient or physician becomes concerned about them or misdiagnoses them as, for example, thrush or lichen planus. No treatment is indicated, other than reassurance.

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29

Gingival drug-induced swelling

Key points

- Gingival swelling can be induced by drugs.
- Swelling typically arises from the interdental papillae and is aggravated by poor oral hygiene.
- Drugs implicated include mainly phenytoin, ciclosporin and calcium channel blockers.

Introduction

A number of disparate drugs can, as an adverse reaction, produce gingival swelling.

Aetiology and pathogenesis

Causal factors may include the following:

- Phenytoin – which is used mainly for the control of grand mal epilepsy. Histology shows marked thickening of epithelium with long overgrowths into the connective tissue. Fibroblasts show increased mitotic activity, but are not increased in number, and the collagen fibre component is not increased.
- Ciclosporin (cyclosporin) – an immunosuppressive drug particularly used to suppress the cell-mediated response after organ transplants, but only one-third of patients may be affected, more commonly children.
- Calcium-channel blockers (especially nifedipine) – which are mainly used as anti-hypertensive agents. Increased numbers of fibroblasts containing strongly sulphated mucopolysaccharides may be demonstrated histochemically; their cytoplasm contains numerous secretory granules, suggesting an increased production of acid mucopolysaccharides. The multidrug resistance 1 (MDR1) gene may modify the inflammatory response to these drugs and thereby play a role in the pathogenesis.
- Amphetamines.

Clinical features

Drug-induced gingival swelling usually starts interdentally. The palatal and lingual gingiva are usually involved less than buccal and labial gingiva. Papillae are

firm, pale and enlarge to form false vertical clefts (Fig. 29.1), which may later involve the marginal and even attached gingiva. The enlargement rarely affects edentulous sites.

The earlier lesions may be softer and redder, sometimes giving the impression of ‘bubbling up’ behind the existing papillae. The enlargement is characteristically firm, pale, and tough with coarse stippling, but these features may take several years to develop. Older lesions may become red if inflamed.

There is no correlation between the extent of overgrowth and the drug dose, its serum level, or the age and sex of the patient. The swelling is aggravated if oral hygiene is poor; there is a positive correlation between the severity of overgrowth and gingival inflammation, plaque score, calculus accumulation and pocket depths.

Excessive body hair growth (hypertrichosis) is commonly associated.

Diagnosis

This is usually a clinical diagnosis.

Management

Treatment of drug-induced swelling often poses problems as the patient often really needs to be on the responsible medication. The patient’s level of plaque control often needs improvement and a chlorhexidine mouthwash may be helpful. Excision of enlarged tissue may be



Fig. 29.1 Ciclosporin-induced gingival swelling

indicated, but difficult if the tissue is very firm and fibrous. Healing may be slow, possibly hampered by infection of the large wound. Unfortunately, the gingival enlargement readily recurs, although this is less likely with meticulous oral hygiene, particularly if the drug has been stopped. The physician may be willing to substitute another drug. Therefore:

- treat predisposing factors
- improve oral hygiene
- gingivoplasty where indicated.

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30

Granulomatous cheilitis

Key points

- Granulomatous cheilitis presents with lip swelling.
- Aetiologies can include orofacial granulomatosis, Crohn's disease, sarcoidosis, infections and lymphoma.
- Accompanying lesions may include ulcers, mucosal 'cobblestones', mucosal tags, gingival enlargements or facial palsy.
- Diagnosis is confirmed by biopsy and other investigations.
- Treatment depends on the cause.

Introduction

Granulomatous cheilitis, also known as cheilitis granulomatosa, is a rare, chronic swelling of the lip due to granulomatous inflammation from a range of aetiologies (Figs 30.1 and 30.2).

Incidence

It is fairly common.

Age

The onset is usually in young adult life and has no racial predilection.

Geographic

No known geographic incidence.

Aetiology

The cause is unknown, but there may be a genetic predisposition. Granulomas in the lamina propria appear to cause lymphatic obstruction and lymphoedema,



Fig. 30.1 Granulomatous cheilitis



Fig. 30.2 Granulomatous cheilitis (same patient as Fig. 30.1)

resulting in swelling (Fig. 30.3). This may be seen in a range of related conditions:

- Melkersson-Rosenthal syndrome (Ch. 43).
- Miescher's cheilitis (Ch. 43).
- Orofacial granulomatosis (OFG) – sometimes from an adverse reaction to various food additives. These additives include cinnamic aldehyde, butylated hydroxyanisole or dodecyl gallate (in margarine), or menthol (in peppermint oil), though these reactions are by no means always relevant; for example, only one out of nine patients in one study had a relationship with such additives.

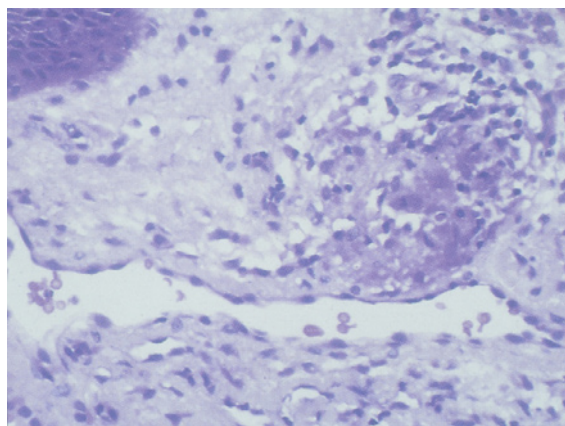


Fig. 30.3 Granulomatous cheilitis



Fig. 30.4 Granulomatous cheilitis

- Crohn's disease.
- Sarcoidosis.
- Infections; rare cases related to tuberculosis or leprosy have been reported. Agents such as *Borrelia burgdorferi* have been discounted as causes.

Clinical features

Cheilitis granulomatosa presents with:

- chronic non-tender swelling and enlargement of one or both lips (Figs 30.4 and 30.5). At the first episode the oedema typically subsides completely in hours or days, but after recurrent attacks the swelling may persist, slowly increases in degree and eventually becomes permanent. The lip involved may feel soft, firm or nodular on palpation. Swellings involve, in decreasing order of frequency, the upper lip and the lower lip and one or both cheeks. Less commonly, lingual, palatal, gingival and buccal involvement also may occur. The forehead, the eyelids or one side of the scalp may be involved as well or in isolation.



Fig. 30.5 Granulomatous cheilitis

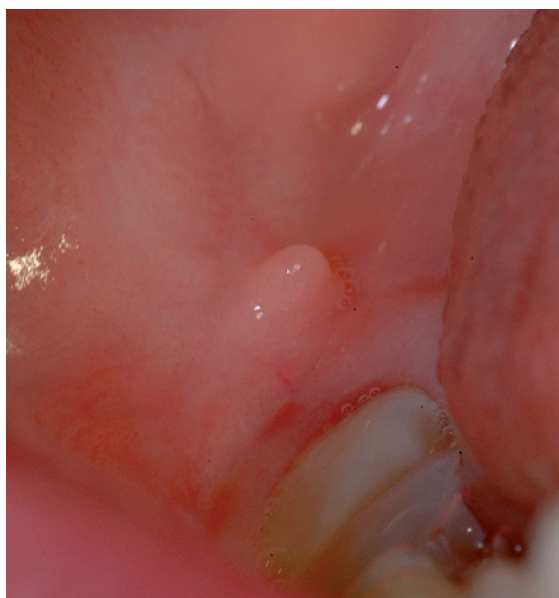


Fig. 30.6 Patient with granulomatous cheilitis showing mucosal tag

The normal lip architecture is eventually altered by the presence of lymphoedema and non-caseating granulomas in the lamina propria. Once chronicity is established, the enlarged lip appears cracked and fissured, with reddish brown discolouration and scaling becomes painful and eventually acquires the consistency of firm rubber. After some years, the swelling may very slowly regress:

- Thickening and folding of the mucosa produces a 'cobblestone' type of appearance and mucosal tags (Fig. 30.6). Purple granulomatous enlargements may appear on the gingiva
- Splitting of the lips and angular stomatitis occurs
- Ulcers appear – classically involving the buccal sulcus where they appear as linear ulcers, often with granulomatous masses flanking them.

The attacks of granulomatous cheilitis are sometimes accompanied by:

- fever and mild constitutional symptoms, including headache and even visual disturbance
- loss of sense of taste and decreased salivary gland secretion
- lymph node enlargement
- central nervous system defects (are sometimes reported), but the significance of the resulting symptoms is easily overlooked as they are very variable, sometimes simulating multiple sclerosis, but often with a poorly defined association of psychotic and neurological features. Autonomic disturbances may occur
- occasionally, cranial nerve deficits (olfactory, facial, auditory, glossopharyngeal, vagus and hypoglossal). Facial palsy occurs in up to 30% of cases. This may precede the attacks of swelling by months or years, but more commonly develops later. Though intermittent at first, the palsy is lower motor neurone type and may become permanent. It may be unilateral or bilateral, and partial or complete and is part of the Melkersson–Rosenthal syndrome (see Ch. 43).
- A fissured or plicated tongue (seen in 20–40% of cases), which is part of the Melkersson–Rosenthal syndrome (see Ch. 43). It is present from birth.

Diagnosis

The early attacks of granulomatous cheilitis may be impossible to clinically differentiate from angioedema, but persistence of the swelling between attacks should suggest the diagnosis. The many causes of oedema of the lips make the diagnosis one based on exclusion, on clinical signs and on histological examination.

Biopsy of the swollen lip or facial tissues is often indicated, but during the early stages may show only lymphoedema and perivascular lymphocytic infiltration. However, with time, the infiltrate usually becomes more dense and pleomorphic and small focal granulomas are formed, which in OFG are indistinguishable from those of Crohn's disease or sarcoidosis. Patch tests and RAST may be indicated to exclude reactions to various foodstuffs or additives. Investigation of the gastrointestinal tract (endoscopy, radiography and biopsy) is mandatory if Crohn's disease is a possibility: endoscopic and histologic intestinal abnormalities are common in younger patients even when there are no gastrointestinal symptoms. Sarcoidosis may be excluded by chest radiography, serum angiotensin converting enzyme, and a gallium scan. If TB is suspected, a tuberculin skin test may also be indicated.

Rare differential diagnoses are from Ascher syndrome associated with blepharochalasia, although the swelling of the lip is caused by redundant salivary tissue and is present from childhood (see Ch. 42), and from lymphoma.

Management

OFG may be an initial manifestation of Crohn's disease and so careful surveillance is recommended. Reactions to dietary components should be sought and possible provoking substances avoided. Elimination diets may be warranted in some patients.

Conservative management usually includes intralesional corticosteroid injections (such as low-volume, high-concentrate, extended-release triamcinolone) or oral clofazimine 100–200mg daily for 3–6 months (hyperpigmentation and raised liver enzymes are adverse effects). Other therapies include non-steroidal anti-inflammatory agents, antibiotics, antimalarials, mast cell stabilizers, tacrolimus, low-dose methotrexate or anti-TNF therapies, but the latter should be used only with caution. Rarely, cheiloplasty is indicated.

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31

Herpesvirus infections

Key points

- Herpesviruses are DNA viruses that are transmitted in saliva, contracted in early life, characterized by latency and reactivated during immunosuppression.
- Herpes simplex virus causes primary herpetic stomatitis and recurrent herpes labialis.
- Herpes zoster varicella causes chickenpox and shingles.
- Epstein-Barr virus causes infectious mononucleosis, and also nasopharyngeal carcinoma, lymphomas and hairy leukoplakia
- Cytomegalovirus causes salivary infections.
- Human herpesviruses 6 and 7 cause rashes
- Human herpesvirus 8 causes Kaposi's sarcoma
- Some herpesviruses are linked to oncogenicity
- A range of antiherpesvirus drugs is now available.

Introduction

Herpesviruses are DNA viruses that are mostly:

- contracted in early life
- transmitted in saliva
- characterized by latency
- reactivated during immunosuppression
- associated with more severe and protracted disorders in patients with compromised immunity, particularly in HIV infection, in cancer patients and in those immunosuppressed after organ grafts.

They include herpesviruses (Table 31.1):

- herpes simplex type 1 (HSV-1)
- herpes simplex type 2 (HSV-2)
- herpes varicella-zoster (VZV)
- Epstein-Barr virus (EBV)
- cytomegalovirus (CMV)
- human herpesvirus type 6 (HHV-6)
- human herpesvirus type 7 (HHV-7)
- human herpesvirus type 8 (HHV-8).

Herpesviruses can sometimes cause malignant tumours (i.e. are *oncogenic*).

Herpes simplex virus

The term 'herpes' is often used loosely to refer to infections with herpes simplex virus (HSV), a ubiquitous virus that commonly produces lesions in the mouth and oropharynx. Primary infection is often sub-clinical between the ages of 2 and 4 years and is a common cause of 'teething'. Herpetic stomatitis (gingivostomatitis) is:

- the primary clinical infection with HSV
- usually caused by HSV-1
- seen mainly in children
- increasingly seen in older patients
- in teenagers it is sometimes due to HSV-2 transmitted sexually
- generally speaking, is caused above the belt (oral or oropharyngeal) by HSV-1, but caused below the belt (genital or anal) by HSV-2.

Incidence

Common, especially in lower socioeconomic conditions.

Age

Primary stomatitis is seen mainly in children and adolescents. Oropharyngeal herpes is seen mainly in adolescents and recurrences are seen mainly in adults.

Sex

Both sexes are affected.

Geographic

Common in children in the developing world. Also seen in adults, especially in the developed world.

Predisposing factors

- Herpes simplex virus is contracted from infected saliva or other body fluids after an incubation period of approximately 4–7 days.
- Close contact with infected individuals, such as in play groups or sexually, predisposes to infection.

Table 31.1
Herpesvirus infections and their possible oral sequelae

Herpesvirus	Abbreviation	Primary infection	Common clinical oral sequelae	Other known possible sequelae, particularly in immunocompromised patients
Herpes simplex	HSV-1	Stomatitis	Herpes labialis	Ulcers Erythema multiforme Bell's palsy
Herpes simplex	HSV-2	Anogenital herpes	Recurrent herpes	Ulcers
Herpes varicella -zoster	VZV	Chickenpox	Zoster	Jaw necrosis
Epstein-Barr virus	EBV	Glandular fever	Fatigue	Hairy leukoplakia Lymphoma
Cytomegalovirus	CMV	Glandular fever	?	Ulcers
Human herpesvirus-6	HHV-6	Rash	?	
Human herpesvirus-7	HHV-7	Rash	?	
Human herpesvirus-8	HHV-8	Rash	Kaposi sarcoma	

- HSV-1 can cause oral or oropharyngeal infection, usually via infection from saliva, and is most frequent and at a younger age in lower socioeconomic groups
- HSV-2 can cause severe oropharyngeal infection, usually via orogenital or oro-anal sexual contact.

Herpes simplex virus anogenital infection is contracted from infected semen, saliva or other body fluids. It is more common in the sexually active and is most frequent amongst female prostitutes (75%) and men who have sex with men (80%). HSV-1 genital infection is usually less common and less severe than HSV-2 infection:

- Patients with immune defects are liable to severe and/or protracted HSV infections.

Aetiology and pathogenesis

- HSV must contact mucosae or abraded skin to initiate infection.
- HSV surface glycoproteins mediate cell attachment and penetration.
- Primary infection is when a susceptible (non-immune) individual develops infection.
- Initial infection occurs when an individual who has antibodies to either HSV-1 or HSV-2 is infected with the other virus type for the first time.
- HSV is neuroinvasive and neurotoxic and infects neurones of dorsal root and autonomic ganglia.
- HSV remains latent thereafter in the ganglion, usually the trigeminal ganglion, but can be reactivated to result in clinical recrudescence (see below).
- HSV is also implicated in Bell's palsy (see Ch. 20) and erythema multiforme (see Ch. 26).



Fig. 31.1 Herpetic stomatitis; ulcers in the palate

Clinical features

Some 50% of primary HSV infections are subclinical. The main features of clinical primary disease are that:

- the mouth or oropharynx is sore (herpetic stomatitis). Other features include:
 - a single episode of oral vesicles, which may be widespread, and break down to leave oral ulcers. These are initially pin-point, but fuse to produce irregular painful ulcers (Fig. 31.1)
 - gingival oedema, erythema and ulceration. Herpetic stomatitis probably explains many instances of 'teething'
- the cervical lymph nodes may be enlarged and tender. Usually, several nodes in the anterior triangle of the neck – especially the jugulodigastric nodes – are enlarged, often bilaterally

Table 31.2**Antiviral therapy of oral herpes simplex infections in the otherwise apparently healthy patient**

Infection	Main antivirals	Therapy
Herpes simplex stomatitis	Aciclovir or valacyclovir	100–200mg aciclovir tablets 5 times daily, or oral suspension (200mg/5ml) 5 times daily or valacyclovir or famciclovir
Recurrent herpes labialis	Penciclovir or Aciclovir	1% penciclovir cream every 2 hours or 5% aciclovir cream every 2 hours

- posterior triangle and nodes elsewhere are not enlarged, unless there are systemic complications or lesions in other sites
- there is no hepatosplenomegaly, unless there are systemic complications or lesions elsewhere
- there is sometimes fever and/or malaise.

Diagnosis

- Herpetic stomatitis should be differentiated from other causes of mouth ulcers (see Ch. 14), especially herpangina, hand, foot and mouth disease, chickenpox and shingles, erythema multiforme and leukaemia.
- Diagnosis is largely clinical.
- Viral studies are occasionally used for diagnosis. These can include:
 - culture – takes days to give a result
 - electron microscopy – is not always available
 - polymerase chain reaction detection of HSV-DNA – is sensitive and rapid, but expensive
 - immunodetection – conventional enzyme-linked immunosorbent assays (ELISA) for serum antibodies have poor sensitivity and specificity, while newer assays based on gG-1 HSV glycoproteins are comparable with Western blot assays. A rising titre of serum antibodies is confirmatory, but only gives the diagnosis retrospectively
 - smears for viral damaged cells – now rarely used.

Management

Although patients eventually have spontaneous remission, treatment is indicated particularly to reduce fever and control pain. Patient information is an important aspect in management:

- Adequate fluid intake is important, especially in children.
- Antipyretics/analgesics, such as paracetamol/acetaminophen or ibuprofen elixir, help relieve pain and fever.
- A soft bland diet may be needed, as the mouth can be very sore.
- Local antiseptics (0.2% aqueous chlorhexidine mouthwashes) may aid resolution of the painful lesions.
- Aciclovir or valacyclovir or famciclovir orally or parenterally is useful mainly in immunocompromised patients or

in the otherwise apparently healthy patient if seen early in the course of the disease (Table 31.2). Antivirals do not reduce the frequency of subsequent recurrences.

Recurrent herpetic infections

Incidence

Up to 15% of the population have recurrent HSV-1 infections.

Age

They occur mainly in adults.

Sex

Both sexes are affected.

Geographic

Herpes labialis is the most common form of recurrence and is seen mainly in sunny climes.

Predisposing factors

Reactivating factors include:

- fever, such as caused by upper respiratory tract infection (hence herpes labialis is often termed 'cold' sores)
- sunlight
- trauma
- immunosuppression.

Aetiology and pathogenesis

HSV-1 is latent in the trigeminal ganglion after primary infection. The virus can be reactivated, is shed into saliva, and there may be clinical recrudescence, recurrently, to produce herpes labialis or, occasionally, intraoral ulceration.

Clinical features

- Features of recurrent herpes labialis are:
 - lip lesions at the mucocutaneous junction (Fig. 31.2)
 - lesions may be preceded by pain, burning, tingling or itching



Fig. 31.2 Herpes labialis

- lesions begin as macules that rapidly become papular, then vesicular for about 48 hours, then become pustular, and finally scab within 72–96 hours and heal without scarring
- widespread recalcitrant lesions may appear in immunocompromised patients.
- Features of recurrent intraoral herpes in apparently healthy patients include:
 - lesions tend to affect the hard palate or gingiva
 - usually there is a small crop of ulcers, which heals within 1–2 weeks
 - lesions are usually over the greater palatine foramen, following a palatal local anaesthetic injection, presumably because of the trauma (Fig. 31.3).
- Features of recurrent intraoral herpes in immunocompromised patients include:
 - lesions may appear as chronic, often dendritic, ulcers
 - lesions are frequently on the tongue dorsum.

Diagnosis

- Differential diagnosis of herpes labialis is mainly from zoster, impetigo, or carcinoma (rarely). Diagnosis is largely clinical, although viral studies are used very occasionally.
- Diagnosis of recurrent intraoral herpes in healthy patients is mainly from zoster. Diagnosis is largely clinical and viral studies are used very occasionally.
- Diagnosis of recurrent intraoral herpes in immunocompromised patients can be difficult since the lesions can mimic many other causes of oral ulceration. Clinical diagnosis tends to underestimate the frequency of these lesions and viral studies may be needed, particularly as there may be co-infection with cytomegalovirus.

Management

- Patient information is an important aspect in management.
- Most patients will have spontaneous remission within 1 week to 10 days, but the condition is both



Fig. 31.3 Recurrent intraoral herpes

uncomfortable and unsightly, and, thus, treatment is indicated.

- Antivirals will achieve maximum benefit only if given early in the disease, but may be indicated in:
 - patients who have severe, widespread or persistent lesions (see Table 31.2)
 - immunocompromised persons.
- Lip lesions in healthy patients may be minimized with penciclovir 1% cream or aciclovir 5% cream applied in the prodrome.
- Lip lesions in immunocompromised patients may require systemic aciclovir or other antivirals, such as valaciclovir or famciclovir (the precursor of penciclovir).
- Recurrent intraoral herpes in healthy patients can be managed with symptomatic treatment with a soft diet and adequate fluid intake, antipyretics/analgesics (paracetamol or ibuprofen elixir), and local antiseptics (0.2% aqueous chlorhexidine mouthwashes). Systemic

Patient information sheet

COLD SORES

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- These are common.
- They are not inherited.
- They are caused by a virus (herpes simplex), which lives in nerves.
- They are infectious and the virus can be transmitted by kissing.
- They may be precipitated by sun exposure, stress, injury or immune problems.
- They have no long-term consequences.
- Blood tests or biopsy may be required.
- Cold sores may be controlled by some antiviral creams or tablets, best used early on.
- Useful website: <http://www.nlm.nih.gov/medlineplus/herpes simplex.html>

aciclovir or other antivirals, such as valciclovir or famciclovir may be indicated for persistent lesions.

- Recurrent intraoral herpes in immunocompromised patients is difficult to manage and systemic aciclovir or other antivirals may well be needed. A soft diet and adequate fluid intake, antipyretics/analgesics (paracetamol elixir) and local antiseptics (0.2% aqueous chlorhexidine mouthwashes) may help.
- Antiviral resistance is becoming a significant problem to immunocompromised persons, especially those with a severe immune defect. Alternative therapies include foscarnet, n-docosanol, idoxuridine, inosine pranobex and tromantadine hydrochloride.

Herpes varicella-zoster virus infections

Chickenpox (varicella)

This is the primary infection with the virus.

Incidence

It is common.

Age

It mainly occurs in children.

Sex

Both sexes are affected.

Geographic

No known geographic incidence, it occurs worldwide.

Predisposing factors

Chickenpox is highly contagious and is spread by droplets.

Aetiology

After this primary infection, the virus remains latent in dorsal root ganglia.

Clinical features

- The incubation period is 14–21 days.
- Some 50% of infections are subclinical.
- Clinical features include:
 - rash – often very prominent and seen mainly on the face and trunk; consists of itchy papules then vesicles, pustules and scabs, in crops
 - fever

- malaise
- irritability
- anorexia
- mouth ulcers – indistinguishable from HSV, but no associated gingivitis
- cervical lymphadenitis.

Diagnosis

The diagnosis is on clinical grounds. A rising antibody titre is confirmatory. Differentiation is from other mouth ulcers, especially herpes simplex and other viral infections.

Management

- Patient information is an important aspect in management.
- Most patients will have spontaneous remission within 1 week to 10 days.
- Management is symptomatic (see page 235); immune globulin or aciclovir are used in immunocompromised patients.
- Antivirals, such as aciclovir can be beneficial, but only if given early in the disease.

Shingles (zoster)

This is recurrence of VZV latent in dorsal root ganglia. The word 'zoster' comes from the Latin for 'belt', since the lesion occurs in a belt-like distribution.

Incidence

It is uncommon.

Age

It occurs mainly in adults, especially the elderly.

Sex

Both sexes are affected.

Geographic

Seen worldwide.

Predisposing factors

Zoster mainly affects the elderly, or immunocompromised, such as in HIV infection, leukaemia or cancer. Zoster has become a fairly common feature in HIV-infected patients treated with HAART (see Chs 5 and 39).

Aetiology

Reactivation of VZV latent in sensory ganglia.

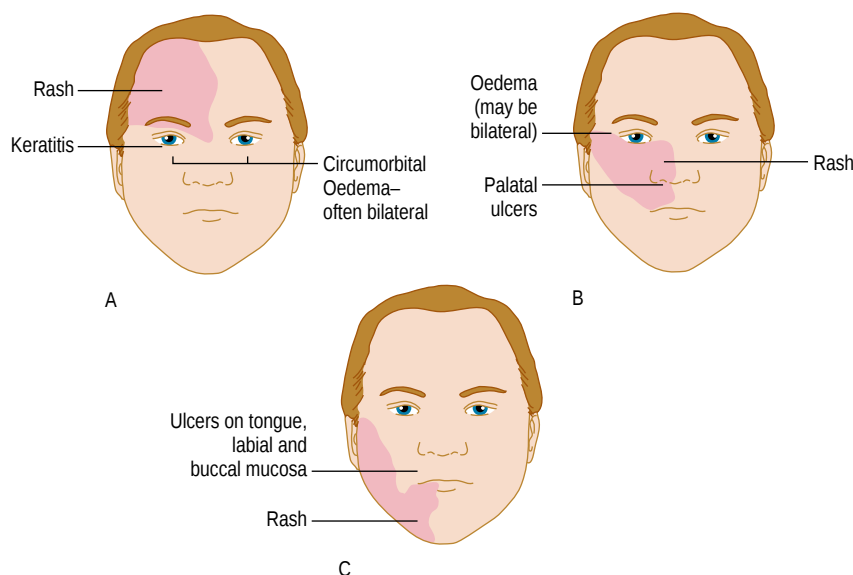


Fig. 31.4 Zoster can affect any of the three divisions of the trigeminal nerve

Clinical features

- The main features are pain and a rash in one dermatome – the area of skin and mucosa supplied by a sensory nerve.
- Most zoster is seen in the thoracic region; 30% is in the trigeminal region.
- Pain occurs before, with and after the rash.
- Rash is unilateral vesiculating then scabbing in dermatome (Fig. 31.4).
- Mouth ulcers are seen in maxillary or mandibular zoster only:
 - mandibular zoster – ipsilateral on buccal and lingual mucosa
 - maxillary – ipsilateral on palate and vestibule.
- Postherpetic neuralgia (see Ch. 38) is the condition when the pain persists long after the rash has healed.

Diagnosis

Diagnosis is clinical; differentiation from toothache and other causes of ulcers, especially HSV, is important.

Management

- Management is with analgesics.
- Aciclovir (high dose) orally or parenterally or valacyclovir or famciclovir may help pain and healing and prevent postherpetic neuralgia.
- Systemic corticosteroids may have a similar effect.
- In ophthalmic zoster an ophthalmological opinion is important, since there can be corneal ulceration.

Epstein–Barr virus infection

EBV is a ubiquitous virus that commonly produces lesions in the mouth and oropharynx.

Incidence

It is common, especially in lower socioeconomic conditions.

Age

Infection is common among young adults (especially students) and is often subclinical.

Sex

Both sexes are affected.

Geographic

Common in the developing world. Also seen in adolescents and adults in the developed world.

Predisposing factors

- EBV is contracted from infected saliva or other body fluids after an incubation period of approximately 20–40 days.
- EBV is found in pharyngeal epithelium and appears in the saliva from patients with infectious mononucleosis and for several months after apparent recovery.
- Close contact with infected individuals, such as sexually, predisposes to infection, which appears to be spread by close oral contact, such as kissing.

- Patients with immune defects are liable to severe and/or protracted infections or the virus may be reactivated, leading to recurrence of infectious mononucleosis or, rarely, producing lymphoproliferative disease.

Clinical features

The clinical features are as follows:

- EBV can cause a glandular fever syndrome termed 'infectious mononucleosis'.
- Infectious mononucleosis is protean in its clinical manifestations which include mainly:
 - lymphadenopathy
 - sore throat
 - fever
 - malaise
 - rashes.

Particular features predominate in some patients:

- In the anginose type of infectious mononucleosis (sore-throat type), the throat is sore with soft palate petechiae and a whitish exudate on oedematous tonsils. Pharyngeal oedema may threaten the airway.
- The glandular type of infectious mononucleosis is characterized mainly by general lymph node enlargement and splenomegaly.
- The febrile type of infectious mononucleosis is characterized mainly by fever.

Recovery can take weeks or months and the virus thereafter remains latent in pharyngeal and/or salivary epithelial cells.

Complications

EBV is also implicated in:

- rashes of a non-allergic nature affecting the extensor surfaces of the limbs in patients taking ampicillin or amoxicillin with infectious mononucleosis
- hairy leukoplakia
- chronic infection, which may cause persistent malaise
- Burkitt's and some other lymphomas
- post-transplantation lymphoproliferative disorder
- nasopharyngeal carcinoma (see Ch. 22).

Diagnosis

- Differentiation from other glandular fever syndromes caused by CMV, HHV-6, HIV or *Toxoplasma* infection is important.
- Investigations are indicated: characteristic of infectious mononucleosis are:
 - mononucleosis – large numbers of atypical mononuclear cells in the blood
 - serological changes such as heterophil antibodies [human antibodies which agglutinate animal (sheep and

horse) erythrocytes and are detectable by the Paul-Bunell (Paul-Bunell-Davidson) or Monospot tests] and antibody to EBV viral capsid antigen (VCA).

Management

- No specific treatment is available, but supportive care should be given.
- Systemic corticosteroids are required if there is pharyngeal oedema severe enough to hazard the airway.

Cytomegalovirus infection

CMV is a ubiquitous herpesvirus that infects most persons at some time during their lives.

Incidence

It is common, especially in lower socioeconomic conditions.

Age

Infection is common among young children and is often subclinical.

Sex

Both sexes are affected.

Geographic

Common in the developing world. Also seen in adolescents and adults in the developed world.

Predisposing factors

- CMV is contracted from infected saliva, urine or other body fluids after an incubation period of approximately 20–40 days.
- Close contact with infected individuals, such as sexually, predisposes to infection.
- CMV can also be transmitted via saliva, blood and transplacentally.
- Patients with immune defects are liable to severe and/or protracted infections, or the virus may be reactivated.

Clinical features

- Infection in normal children or adults is usually asymptomatic, but the virus thereafter remains latent in the body.
- Symptomatic CMV infection in otherwise apparently healthy children and adults causes the CMV mononucleosis syndrome of headache, back and abdominal pain, sore throat, fever and atypical lymphocytosis, but with a negative Paul-Bunell test ('infectious lymphocytosis').

- Transplacental infection may cause abortion, learning disability or other defects, and the affected child excretes CMV in urine for months or years after birth and is a major reservoir of the virus.
- Immunocompromised patients may also be infected with CMV, or latent CMV may be reactivated. They also excrete the virus. In these patients, such as those with renal transplants and patients with HIV/AIDS, CMV acts as an opportunistic infection and may cause serious disease involving the lungs, liver, gastrointestinal tract, CNS and eyes.

Diagnosis

- Differentiation from other glandular fever syndromes caused by EBV, HHV-6, HIV or *Toxoplasma* infection is important.
- Virus isolation and serology may be of value in the diagnosis.

Management

Treatment is usually symptomatic, although antivirals, such as ganciclovir are indicated in the immunocompromised host.

Other human herpesviruses

- HHV-6 is usually associated with a rash in children, but has also been implicated in some cases of:
 - glandular-fever-type syndromes (see Ch. 3)
 - facial palsy.
- HHV-7 is not of any known relevance to oral health.
- HHV-8 is a recently discovered DNA virus transmitted mainly sexually and strongly associated with Kaposi sarcoma.

Websites

<http://www.herples.com/overview.shtml>
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Key points

- Lichen planus is an immunologically mediated mucocutaneous disorder.
- Aetiological factors include drugs, dental materials, graft-versus-host disease and other factors.
- Lesions of lichen planus are typically bilateral and affect the buccal mucosae.
- Diagnosis is clinical supported by biopsy
- Management usually includes topical corticosteroids.

Introduction

Lichen planus (LP) is an inflammatory autoimmune-type of mucocutaneous disease that can affect stratified squamous epithelia – the skin, oral mucosa and genitalia (Fig. 32.1).



Fig. 32.1 Papuloreticular lichen planus

Incidence

Lichen planus is not uncommon and has a prevalence of the order of 1%.

Age

It usually affects persons between the ages of 30 to 65 years.

Sex

There is a slight female predisposition to LP.

Geographic

LP is seen worldwide.

Predisposing factors (Fig. 32.2)

- There is no definitive immunogenetic basis yet established for LP, but studies have reported various HLA associations:
 - in oral LP: an increase in HLA B15, Bw57, B5, B7, BX, DR2 and HLA-te22, and a decrease in the frequency of HLA-DQ1, DR4 and B18
 - in patients with hepatitis C virus-associated oral LP, an increased frequency of HLA-DR6
 - in patients with carbohydrate metabolism disorders and oral LP: an increased frequency of HLA B16, B2 and B40.
 - in cutaneous LP: an increase in HLA-DR1 (mainly HLA-DRB1*0101), DQ1, DR3 or DR9
- Stress has been widely held to be an important aetiological factor in LP, but, of the remarkably few studies, most have not objectively examined stress. A statistically significant difference was, indeed, found in the psychological profiles of patients affected by LP – who have a tendency to be depressed and anxious, but the chronic discomfort that can afflict patients with LP can of course itself be a stressing factor and

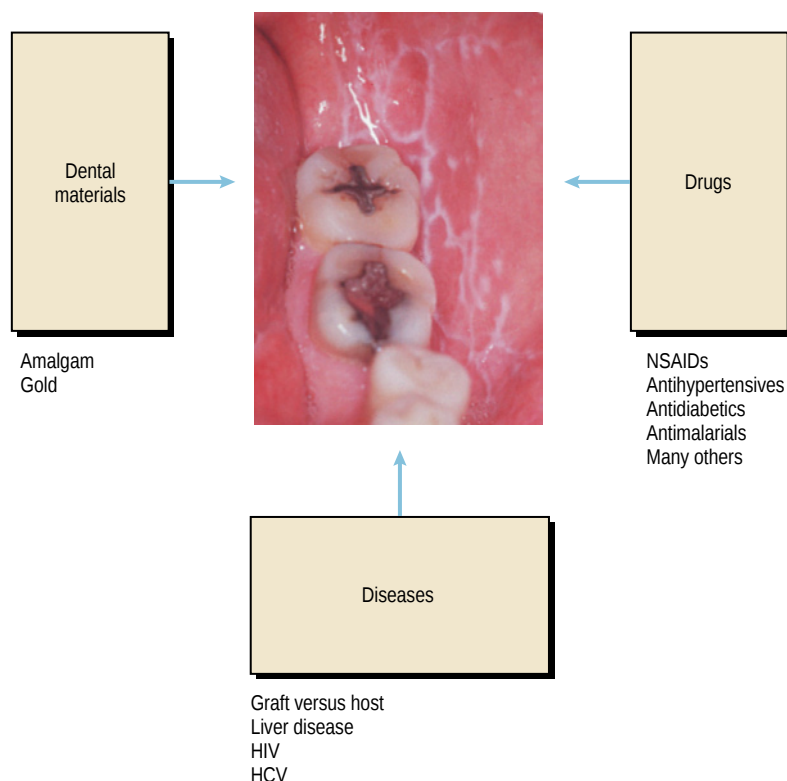


Fig. 32.2 Factors implicated in pathogenesis of lichen planus

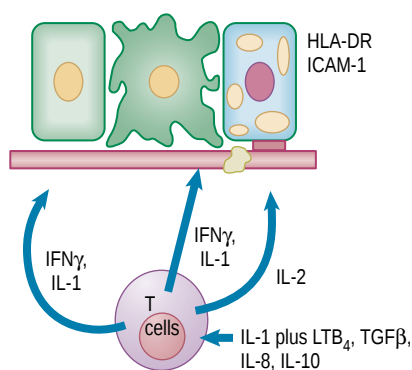


Fig. 32.3 Aetiopathogenesis of lichen planus. IL, interleukin; IFN, interferon; LTB, leukotriene; TGF, transforming growth factor

may partially explain some cases in which this association has been documented.

- Lesions similar to LP, termed 'lichenoid lesions', are sometimes caused by:
 - dental restorative materials (mainly amalgam and gold)

- chronic graft-versus-host disease, seen in bone marrow (haemopoietic stem cell) transplant patients
- infection with hepatitis C virus in some populations, such as those from southern Europe and Japan
- a variety of other systemic disorders, such as hypertension and diabetes, but this is often a manifestation of a reaction to the drugs used
- drug and vaccine use: antidiabetic drugs; antirheumatic drugs (non-steroidal anti-inflammatory agents mainly, but also others); antihypertensive agents, such as angiotensin-converting enzyme inhibitors, beta-blockers, thiazides and diuretics; antimalarials, such as quinacrine; many other drugs; occasionally, hepatitis B vaccine.

Aetiology and pathogenesis

LP is not a classical autoimmune disorder, but involves immunologically mediated epithelial damage (Fig. 32.3):

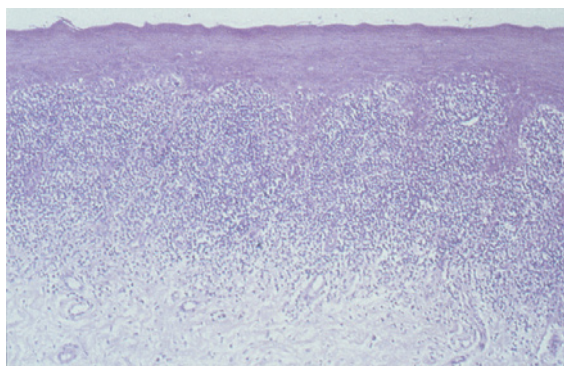


Fig. 32.4 Histopathology



Fig. 32.5 Papuloreticular lichen planus

- The antigen(s) that may be responsible for LP is unknown, but preliminary studies have revealed a LP-specific epidermal antigen in some epithelial cells. Studies looking for any causal bacteria, fungi and viruses have proved negative.
- The earliest features of LP are changes in, and close to, the basal epithelium. The appearance of antigen-processing cells (Langerhans cells) is one of the first observable changes.
- A band-like dense mononuclear inflammatory cell infiltrate, mainly of T CD8⁺ cells, appears in the upper lamina propria, representing a local cell-mediated immunological response (Fig. 32.4).
- The basal epithelial cells undergo flattening and hydropic changes and intercellular spaces appear, with splitting of epithelium away from the basement membrane – termed basal cell liquefaction. This represents apoptosis (controlled cell death), probably caused by the T-cell production of cytokines such as tumour necrosis factor- α (TNF- α) and interferon- γ (IFN- γ). Atrophy and even erosions can appear – leading to discomfort and the appearance of red lesions and/or ulceration.
- Degeneration and premature cell death of these basal keratinocytes leads to the appearance of



Fig. 32.6 Lichen planus of the plaque type, resembling leukoplakia

round or ovoid ‘colloid bodies’ (also termed cytooid, globular, hyaline, Civatte and Sabouraud’s bodies) in the epithelial spinous layer and in the lamina propria. Immune deposits (typically fibrin and sometimes IgM) are seen in colloid bodies and at the basement membrane zone, but they probably represent non-specific exudation and not autoantibodies.

- The rest of the epithelium appears to react with thickening of the spinous layer (acanthosis) and granular cell layer (hyperparakeratosis) or hyperorthokeratosis – which accounts for the clinical white lesions.
- The rete ridges adopt a ‘saw tooth’ configuration (more commonly in skin than oral lesions).

Clinical features

- Six clinical types of oral LP have been reported:
 - Reticular, a network of raised white lines or striae (reticular pattern)
 - Papular, white papules (Fig. 32.5)
 - Plaque-like, simulating leukoplakia (Fig. 32.6)
 - Red atrophic areas – LP is one of the most common causes of desquamative gingivitis (Fig. 32.7).
 - Erosive/ulcerative – persistent, irregular, and painful erosions with a yellowish slough (this type is less common) (Fig. 32.8).
 - Bullous.

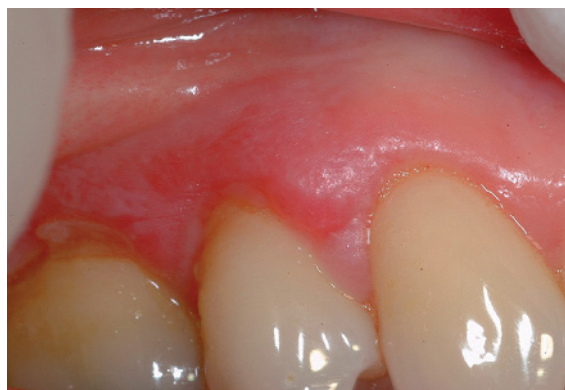


Fig. 32.7 Atrophic lichen planus



Fig. 32.8 Erosive lichen planus

- LP is often asymptomatic, but there may be soreness from atrophic areas of thin, red mucosa or erosions. White lesions are usually asymptomatic, however; mild oral discomfort or burning sensations are the most common complaints in symptomatic cases.
- LP typically results in lesions which are:
 - mostly white
 - reticular, but may be papular or plaque-like and associated with red atrophic areas in the posterior buccal mucosa bilaterally
 - occasionally on the dorsum of the tongue where it may be reticular, papular or plaque-like and associated with red atrophic or erosive areas
 - on the gingiva. This may be a white lacework of fine white lines and papules. A 'desquamative gingivitis' may also develop in about 25% of patients with erosive LP and can be the initial or the only sign of oral involvement
 - on the lips – usually a white lacework of fine white lines and papules (Fig. 32.9)
 - rarely on the palate.



Fig. 32.9 Lichen planus on lips



Fig. 32.10 Pigmentary incontinence in lichen planus

Prognosis

Often the onset of lichen planus is slow, taking months to reach its peak. It often clears from the skin within 18 months, but in a few people persists for many years. Oral lesions are often persistent. In people with dark skin there may be pigmentary incontinence with dark areas appearing (Fig. 32.10).

Malignant potential

Lichenoid lesions have a small premalignant potential – probably of the order of <1%, and predominantly in non-reticular lesions (Fig. 32.11).

Extraoral lesions

Lichen planus may also cause lesions elsewhere, including:

- skin: rash characterized by lesions, which are:
 - purple



Fig. 32.11 Carcinoma arising in non-reticular lichen planus



Fig. 32.12 Skin papules in lichen planus

- polygonal
- pruritic (itchy)
- papules – often crossed by fine white lines (Wickham striae) (Fig. 32.12)

and is most often seen on the:

- front (flexor surface) of the wrists
- lower back
- ankles and shins.

Trauma may induce new skin lesions (Koebner phenomenon):

- Skin appendages: in 10% of cases there is nail involvement, usually a minor change (Fig. 32.13), but occasionally resulting in shedding or destruction of the nail. The scalp is uncommonly affected, but permanently bald patches may develop.
- Genital mucosae:
 - The 'vulvovaginal-gingival syndrome' is the association of oral LP with vulvovaginal lesions of LP.



Fig. 32.13 Nail changes in lichen planus

This is fairly common and there is coincident onset of gingival and genital lesions in about half the reported patients, the remainder developing lesions at both sites within 2 years. The oral lesions mainly affect the labial gingivae.

- The penolingival syndrome is less common and less incapacitating.

Diagnosis

Lichen planus is often fairly obviously diagnosed from the clinical features, but it can closely simulate other conditions, such as:

- lupus erythematosus
- chronic ulcerative stomatitis
- keratosis
- carcinoma.

Lichenoid lesions that may need to be excluded include:

- drug-induced lesions
- dental-material-induced lesions (Fig. 32.14)
- diabetes mellitus
- graft-versus-host disease
- hepatic disease or hepatitis C virus infection
- HIV.

Lichenoid lesions clinically resemble LP, but may:

- be unilateral
- be associated with erosions
- resolve on discontinuation of any offending drug.

Skin testing for hypersensitivity to drugs or dental materials is only rarely of clinical value.

Lichenoid lesions histopathologically are more likely than LP to be associated with:

- a mixed cellular infiltrate including plasma cells and eosinophils



Fig. 32.14 Lichenoid lesions related to an amalgam restoration

- a deeper infiltrate
- a perivascular infiltrate
- parakeratosis
- colloid bodies in the epithelium
- basal cell autoantibodies.

The firm diagnosis of LP, therefore, relies upon biopsy and histopathological examination of lesional tissue, occasionally aided by direct immunostaining. However, often the histological and immunological findings revealed are no more than 'consistent with lichen planus', but this at least serves to exclude more dangerous conditions.

Management

Patient information is an important aspect in management. Unfortunately, although the natural history of cutaneous LP is one often of remission, oral LP remits only in a few patients, and thus treatment is indicated for symptomatic LP (Algorithm 32.1).

Predisposing factors should be corrected:

- It may be wise to consider removal of dental amalgams if the lesions are closely related to these, or unilateral. Unfortunately, no tests, such as patch tests, will reliably indicate which patients may benefit.
- The physician should be consulted if there is HCV infection or other systemic background, or if drugs are implicated.
- Improvement in oral hygiene may result in some subjective benefit. Thus, good oral hygiene should be maintained. Chlorhexidine or triclosan mouthwashes may help.
- Symptoms can often be controlled with topical medication, such as topical corticosteroids and topical tacrolimus. Antifungals may help, especially where there is candidal superinfection.

Patient information sheet

LICHEN PLANUS

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a common condition.
- The cause is unknown.
- Children do not usually inherit it from parents.
- It is not thought to be infectious.
- Lichen planus is sometimes related to drugs, dental fillings or other conditions.
- Some patients have the condition on the skin or elsewhere.
- Blood tests and biopsy may be required.
- The condition tends to persist in the mouth.
- Lichen planus can be controlled, but rarely cured.
- Most lichen planus is benign.
- Some forms of lichen planus may rarely, after years, lead to a tumour. In this case, you should get yourself checked regularly if the specialist advises.
- Useful websites:
 - <http://www.tambcd.edu/lichen>
 - <http://www.nlm.nih.gov/medlineplus/oralcancer.html>
 - <http://www.tambcd.edu/lichen/>
 - <http://www.aad.org/pamphlets/lichen.html>

Severity-dependent treatment

Mild LP

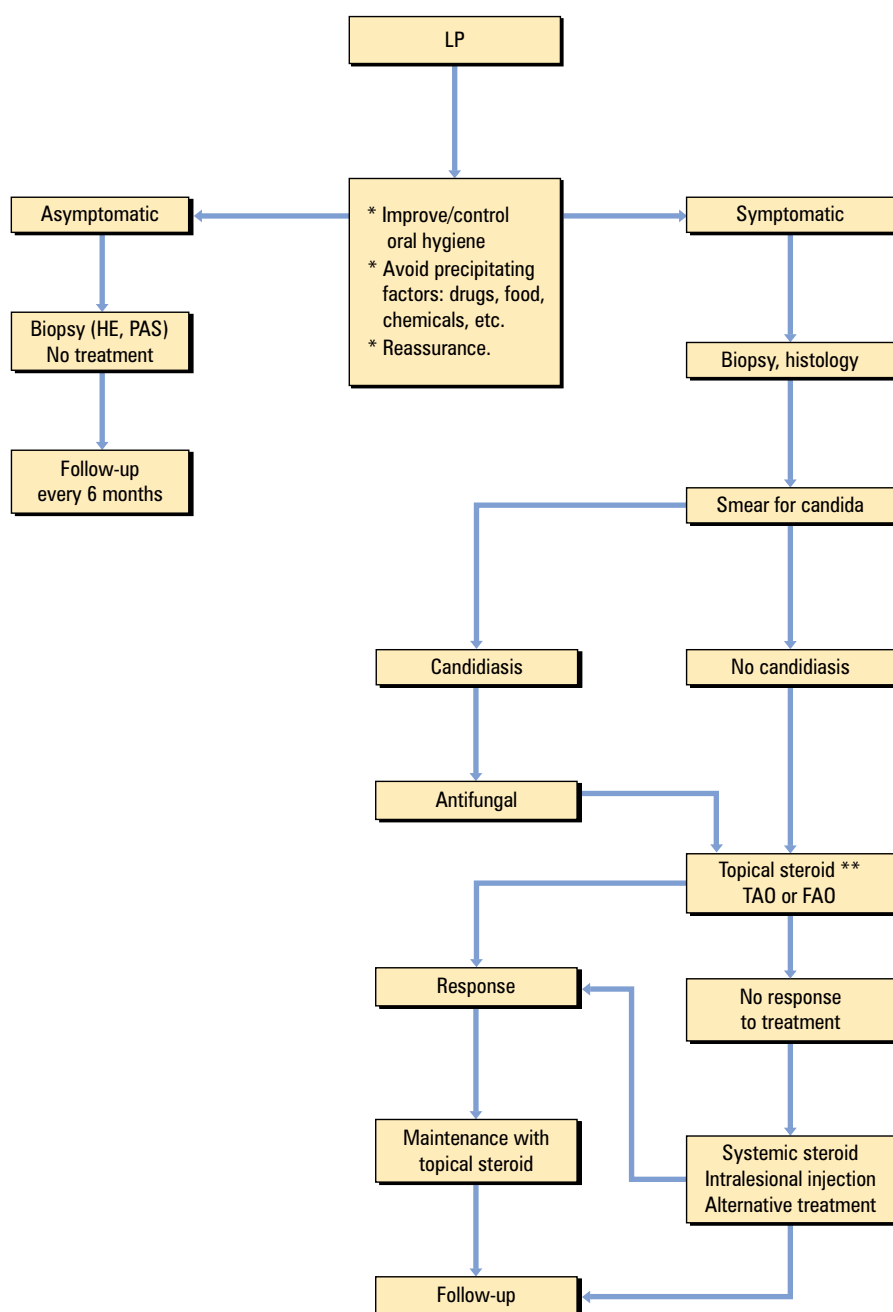
Topical corticosteroids are the mainstay of therapy, although erosive and gingival lesions are often recalcitrant. High potency corticosteroids, such as clobetasol, fluocinonide or fluticasone, may initially be employed and should then be changed to a lower potency drug (e.g. hydrocortisone hemisuccinate, triamcinolone acetate or fluocinolone). Topical creams or pastes can be applied in a suitable customized tray or veneer to be worn at night.

Moderate LP

If there is severe or extensive oral involvement, topical ciclosporin or tacrolimus may be of significant benefit, often being used along with a high or super potent topical steroid. This regimen is useful in the management of LP-related desquamative gingivitis recalcitrant to other therapies.

Severe LP

In severe LP in multiple sites, patients may require systemic corticosteroids, azathioprine, cyclophosphamide, hydroxychloroquine, acitretin, thalidomide or ciclosporin. Dapsone is occasionally effective.



HE = Haematoxylin and eosin

PAS = Periodic Acid-Schiff

**TAO = Triamcinolone acetonide 0.1% in orabase

FAO = Fluocinolone acetonide 0.1% in orabase/solution

Algorithm 32.1 Management of lichen planus

Failure to respond to treatment

If LP fails to respond to topical measures, systemic immunomodulators may be required, under specialist supervision. These include the following:

- Systemic corticosteroids, e.g. prednisolone (see Ch. 5).
- Other immunomodulatory agents (e.g. azathioprine, ciclosporin, interferon).
- Thalidomide may be effective against severe LP. However, it is rarely indicated since it is teratogenic and can produce neuropathies.
- Other therapies for LP include retinoids, dapsone, low molecular weight heparin, efalizumab and many others, but either their efficacy has not been well proven or they have unacceptable adverse effects.

Patients with non-reticular lichen planus should be monitored to exclude development of carcinoma. Tobacco, betel and alcohol use should be minimized.

Websites

<http://www.aarda.org/indexf.html>

The International Oral Lichen Planus Support Group <http://www.tambcd.edu/lichen>

<http://www.aarda.org/indexf.html>

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Key points

- Odontogenic cysts are usually asymptomatic and detected on routine imaging:
 - Periapical cysts are the most common
 - Dentigerous cysts are second most common
 - Keratocystic odontogenic tumours are the third most common cysts, are great mimics, may recur after removal as well as behave aggressively and are sometimes associated with Gorlin syndrome.
- Odontogenic tumours may be asymptomatic and detected on routine imaging:
 - Most odontogenic tumours (75%) are odontomas, benign hamartomas or developmental anomalies of tooth tissues
 - Ameloblastoma is the next most common, may recur after removal and behave aggressively
 - Benign odontogenic tumours are 100 times more common than malignant ones.

Introduction

Odontogenic cysts and tumours are defined as lesions of the jaws and gingiva derived from odontogenic epithelium. The aetiology of these lesions is quite unclear.

Odontogenic cysts

A cyst is a pathological cavity having liquid, semi-liquid or gaseous contents. It is frequently, but not always, lined with epithelium.

Most cysts of the jaws arise from odontogenic epithelium. These are relatively common lesions – most are inflammatory cysts (about 55% of all jaw cysts), dentigerous cysts (22%) or odontogenic keratocysts (19%).

There is an overall male predominance and the mandible is affected three times as commonly as the maxilla.

Aetiology and pathogenesis

The main pathogenic factors include the following:

- Epithelial proliferation – either stimulated by inflammation in the case of radicular cysts, or occurring with genetic stimulation in the case of keratocysts and probably the glandular odontogenic cyst.
- Hydrostatic or osmotic factors – may play a part in cyst growth since the cyst wall acts as a semipermeable membrane.
- Keratin formation – may be prominent in keratocysts.
- Bone resorbing factors, such as prostaglandins and collagenase.

Clinical features

Odontogenic cysts are often asymptomatic, and their discovery is usually an incidental finding on radiography. They are generally slow-growing and may reach a large size before they give rise to symptoms, such as:

- swelling; cysts in bone initially produce a smooth bony hard lump with normal overlying mucosa but, as the bone thins, it may crackle on palpation rather like an egg shell (termed 'egg shell cracking'). When the overlying bone is resorbed, the cyst may show through as a bluish fluctuant swelling (Fig. 33.1)
- discharge; usually into the mouth
- pain; due to secondary infection.

Most odontogenic cysts are benign, but occasionally tumours or squamous cell carcinomas may arise within.



Fig. 33.1 Odontogenic cyst

Diagnosis

The diagnosis is based on an adequate history, clinical examination and appropriate investigations, such as pulp vitality testing and radiographs (both intraoral and extraoral) of associated teeth, aspiration and analysis of cyst fluids, and histopathology.

Management

Odontogenic cysts are managed either by enucleation or by marsupialization:

- Enucleation is the complete removal of the cyst. The benefit of enucleation is that all the cyst tissue is available for histological examination and the cyst cavity will usually heal uneventfully with minimal aftercare. Enucleation is potentially problematic however, if the cyst involves the apices of adjacent vital teeth, as the surgery may deprive the teeth of their blood supply and render them non-vital.
- Marsupialization is the partial removal of the cyst. Marsupialization requires considerable aftercare and good patient cooperation in keeping the cavity clean whilst it resolves. In order to keep the cavity open, a 'bung' or acrylic plug is usually inserted in the opening, often attached to a denture or acrylic splint. The bung stops most food collecting in the cavity, but the cavity must still be syringed by the patient after each meal. Healing is slower than after enucleation: marsupialized cyst cavities may take up to 6 months to close down to the extent of becoming 'self-cleansing'. The other disadvantage of marsupialization is that not all the cyst lining is available to histopathological examination, and this may lead to misdiagnosis.

Inflammatory cysts

Inflammatory cysts are by far the most common of all jaw cysts and arise in association with a non-vital tooth. They include the following:

- Radicular cyst (dental or periapical cyst) – where the cyst is associated with the apex of a non-vital tooth. Occasionally, a radicular cyst may develop on the lateral aspect of a root, where the stimulus has been an inflammatory reaction arising from necrotic pulp in a lateral root canal. Radicular cysts are seen especially where:
 - a non-vital pulp is infected
 - endodontic treatment has failed
 - a root has fractured and there is a perforation
 - a root is retained.
- Residual cysts – where one of the above inflammatory cysts (usually a radicular cyst) remains after the removal of the non-vital tooth from which it arose.



Fig. 33.2 Developing radicular cyst

The epithelial lining of inflammatory cysts is derived from the rests of Malassez, which proliferate to produce thick irregular, often incomplete squamous epithelium, with granulation tissue forming the cyst wall in the denuded areas (Fig. 33.2). Depending on the nature of the inflammatory response, there may be areas of chronic inflammation, or acute inflammation with abscess formation. Cholesterol crystal clefts are often present and mucous cells may be found. The cyst fluid is usually watery, but may be thick and viscid with cholesterol crystal clefts giving it a shimmering appearance. The cysts have capsules of collagenous fibrous connective tissue and cause bone resorption and may become quite large.

Bacterial endotoxins may initiate epithelial proliferation together with complement activation and T lymphocyte infiltration, which release contributory inflammatory cytokines-interleukins, especially IL-1 and IL-6, in particular. Osmosis plays a role in cyst expansion. Prostaglandins, collagenases and matrix metalloproteinases plus gene products NFkappaB ligand (RANKL) and osteoprotegerin (OPG) appear to be associated with the bone destruction both in periapical cysts and periapical granulomas. The Runx2 (core-binding protein [cbfa]1/polyoma enhancer-binding protein [pebp]2alphaA) a DNA-binding transcriptional molecule expressed in osteoprogenitor cells, and transforming growth factor (TGF-β2) are involved in the new bone formation.

Diagnosis

The diagnosis is based on an adequate history, clinical examination and appropriate investigations, such as pulp vitality testing and radiographs (both intraoral and extraoral) of associated teeth, aspiration and analysis of cyst fluids, and histopathology. Protein p63 expression may be useful to identify cyst types with a more aggressive and invasive phenotype.

Management

The treatment of inflammatory cysts depends on whether the involved non-vital tooth is to be retained. Conventional intra-canal endodontic treatment will often

lead to the resolution of very small radicular cysts, but regular radiographic review is necessary until there has been complete resolution of the cyst. If, when the tooth has been root-filled, the cyst does not resolve, or if the cyst is of such a size that it is unlikely to resolve with endodontic treatment alone, surgery is indicated – either enucleation or marsupialization.

Developmental cysts

Dentigerous (follicular) cyst

Dentigerous cyst is the second most common odontogenic cyst. This develops within the normal dental follicle that surrounds an unerupted tooth, or from degeneration of the stellate reticulum, or an accumulation of fluid between the layers of the reduced enamel epithelium. The lining typically consists of flattened stratified epithelium.

Clinical features

The dentigerous cyst is most frequently found in areas where unerupted teeth are found – mandibular third molars, maxillary third molars and maxillary canines, in decreasing order of frequency. These cysts may grow to a large size, displace the tooth with which they are associated, or rarely cause resorption of adjacent tooth roots.

Diagnosis

Diagnosis is usually made by clinical and radiographic assessment – when the follicular space exceeds 5mm from the crown it is likely that a cyst is present. However, odontogenic keratocysts and ameloblastomas may occasionally mimic the radiological appearances of follicular cysts. Aspiration may be helpful in differentiating from other lesions.

Management

Treatment may be either marsupialization, allowing the tooth to erupt, or enucleation, with removal of the associated tooth. Rarely ameloblastomas arise within a dentigerous cyst, and squamous cell carcinoma may also appear.

Eruption cysts

Eruption cysts are considered as minor soft tissue forms of dentigerous cysts. In these cases, the involved teeth are usually prevented from eruption by dense fibrous tissue overlying them. They often burst spontaneously before eruption of the associated tooth, and only rarely require excision if impeding normal eruption. If thought

to be necessary, a narrow window can be excised over the erupting tooth.

Keratocystic odontogenic tumour (KCOT: odontogenic keratocyst; OKC; primordial cyst)

The KCOT is the least common, but most dangerous odontogenic cyst. KCOT can be associated with the naevoid basal cell carcinoma syndrome (NBCCS: Gorlin syndrome) (see Ch. 43). They may be associated with the PTCH gene on chromosome 9. By definition, KCOTs develop instead of a tooth, arising from the dental lamina or remnants, while some, particularly in the posterior mandible, may develop from basal cell off-shoots or hamartomas from the overlying gingival epithelium. The epithelium may harbour *patched* (PTCH) mutations, leading to constitutive activity of the embryonic *Hedgehog* (Hh) signalling pathway.

KCOT growth has been attributed to osmolality of the cyst fluid, and to various bone-resorbing factors, including collagenases, interleukin 1, matrix metalloproteinases and parathyroid-hormone-related protein.

Clinical features

The KCOT is a great mimic; it may have many clinical appearances, and may be seen over a wide age range. Most involve the mandibular angle and may expand to occupy the major part of the ramus as a radiolucent lesion. They may sometimes be multilocular. They may resorb the cortical plates and expand into the soft tissues, envelop unerupted teeth giving a dentigerous appearance or displace teeth but not resorb them. KCOTs are generally painless, and often grow to a large size before giving rise to symptoms, unless they become secondarily infected.

Diagnosis

The diagnosis of KCOT is essentially on histological grounds. Diagnosis may be suggested by clinical features supported by imaging, and aspiration and estimation of soluble protein level in aspirated cyst fluid may be an aid to the diagnosis, since a protein level of less than 4g/100ml suggests KCOT, whereas a value over 5g/100ml suggests a radicular or dentigerous cyst, or rarely a cystic ameloblastoma. The demonstration of keratin squames in an aspirate is virtually diagnostic of a KCOT.

The cyst lining usually has a characteristic appearance of a regular keratinized stratified squamous epithelium, commonly five to eight cell layers thick and without rete pegs (Figs 33.3 and 33.4). There is a well-defined basal layer predominantly of columnar, but occasionally cuboidal, cells. Desquamated keratin is often present within the cyst lumen and the fibrous wall is usually thin. KCOT are often multilocular.



Fig. 33.3 Keratocystic odontogenic tumour (low power view)

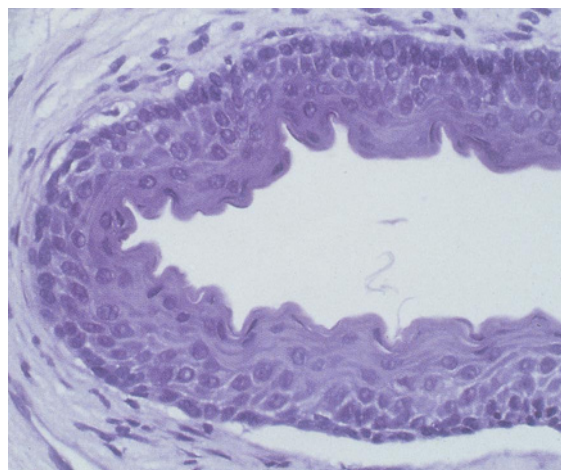


Fig. 33.4 Keratocystic odontogenic tumour (high power)

Management

Gorlin syndrome should be excluded – especially if the lesions are bilateral and/or in young people. Although there is some dispute over the most appropriate treatment for keratocysts, all authors agree that the cyst lining should be meticulously removed. Small unilocular lesions should be thoroughly enucleated. Large or multiloculated cysts should be excised with a margin of surrounding bone. KCOT's tend to recur following removal; recurrence rates can be as high as 60%. Long-term clinical and radiographic follow-up is mandatory as recurrences may occur many years after initial treatment.

One KCOT variant (orthokeratinized odontogenic cyst) is almost always found in a dentigerous association, usually around the mandibular third molar. It does not have a hyperchromatic basal layer and produces only orthokeratin, is not associated with basal cell naevus syndrome and acts much less aggressively.

Other odontogenic cysts

These cysts are uncommon and their pathogenesis is far from clear. They include:

- glandular odontogenic cyst (GOC; sialo-odontogenic cyst) – usually presents in the anterior mandible as a painless, slow-growing swelling and a large, multiloculated, well-defined radiolucency. It contains mucous cells and duct-like structures that may mimic central mucoepidermoid carcinoma. Characteristic histopathological features include epithelial spherules/‘knobs’/whorls, cuboidal eosinophilic cells, goblet cells, intraepithelial glandular/microcystic ducts, variations in lining width, ciliated cells and mucous pools/mucous-lined crypts, which, with expression of p53 and Ki67, may aid the diagnosis. GOC tends to be aggressive and may recur following curettage

- gingival cysts of adults – which arise from epithelial rests in the gingivae and are found only in soft tissue in the lower premolar areas
- gingival cysts of infants – which arise from remnants of the dental lamina and are located in the corium below the surface epithelium. They are generally asymptomatic. Bohn nodules and Epstein pearls are similar lesions with which gingival cysts sometimes are confused (see Ch. 43)
- developmental lateral periodontal cysts – which are most commonly associated with the mandibular premolar area and occasionally the maxillary anterior region and arise from the postfunctional dental lamina. As described earlier, cysts of inflammatory origin are found to lie on the lateral aspect of a non-vital tooth, and must be distinguished from a developmental lateral periodontal cyst
- paradental cysts are also of inflammatory origin and are most frequently found on the lateral aspect of the roots of partially erupted mandibular third molars where there is an associated history of pericoronitis.

Treatment of all these cysts is generally by enucleation.

Odontogenic tumours

Odontogenic tumours may consist predominantly of odontogenic epithelium, ectomesenchyme, or both (Box 33.1). Enamel, dentine and their precursors are also present in a number of other lesions and then their presence is usually indicated by inclusion of the prefix ‘odonto’ (e.g. ameloblastic fibro-odontoma, odontameloblastoma, ameloblastic odontosarcoma):

- Odontogenic tumours consisting predominantly of epithelium arise from odontogenic epithelium, but

► Box 33.1

WHO classification of odontogenic tumours*

Malignant tumours

- Odontogenic carcinomas:
 - metastasizing (malignant) ameloblastoma 9310/3
 - ameloblastic carcinoma – primary type 9270/3
 - ameloblastic carcinoma – secondary type (dedifferentiated), intraosseous 9270/3
 - ameloblastic carcinoma – secondary type (dedifferentiated), peripheral 9270/3
 - primary intraosseous squamous cell carcinoma – solid type 9270/3
 - primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumour 9270/3
 - primary intraosseous squamous cell carcinoma derived from odontogenic cysts 9270/3
 - clear cell odontogenic carcinoma 9341/3
 - ghost cell odontogenic carcinoma 9302/3
- Odontogenic sarcomas:
 - ameloblastic fibrosarcoma 9330/3
 - ameloblastic fibrodentino- and fibro-odontosarcoma 9290/3

Benign tumours

- Odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme:
 - ameloblastoma, solid/multicystic type 9310/0
 - ameloblastoma, extraosseous/peripheral type 9310/0
 - ameloblastoma, desmoplastic type 9310/0
 - ameloblastoma, unicystic type 9310/0
 - squamous odontogenic tumour 9312/0
 - calcifying epithelial odontogenic tumour 9340/0
 - adenomatoid odontogenic tumour 9300/0
 - keratocystic odontogenic tumour 9270/0
- Odontogenic epithelium with mature, fibrous stroma without odontogenic ectomesenchyme:
 - ameloblastic fibroma 9330/0
 - ameloblastic fibrodentinoma 9271/0
 - ameloblastic fibro-odontoma 9290/0
 - odontoma: 9280/0
 - odontoma, complex type 9282/0
 - odontoma, compound type 9281/0
 - odontoameloblastoma 9311/0
 - calcifying cystic odontogenic tumour 9301/0
 - dentinogenic ghost cell tumour 9302/0
- Mesenchyme and/or odontogenic ectomesenchyme with or without odontogenic epithelium:
 - odontogenic fibroma 9321/0
 - odontogenic myxoma/myxofibroma 9320/0
 - cementoblastoma 9273/0
- Bone-related lesions: 9262/0
 - ossifying fibroma
 - fibrous dysplasia
 - osseous dysplasias
 - central giant cell lesion (granuloma)
 - cherubism
 - aneurysmal bone cyst
 - simple bone cyst

Other tumours

- Melanotic neuroectodermal tumour of infancy 9363/0

*Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded/0 for benign tumours,/3 for malignant tumours and/1 for borderline or uncertain behaviour.

it is uncertain whether this epithelium is derived from the enamel organ itself, the remnants of the dental lamina (cell rests of Serre) or Hertwig's root sheath (cell rests of Malassez), the epithelium of odontogenic cysts (particularly the dentigerous cyst), or from the oral mucosa.

- Odontogenic tumours composed of odontogenic connective tissue originate from the ectomesenchymal portion of the tooth germ, either from the dental papilla or the dental follicle.
- Odontogenic tumours of mixed origin consist both of odontogenic epithelium and ectomesenchyme and, during the period of active growth contain both ameloblastic epithelium and odontoblastic tissue, but, when completely developed, consist principally of enamel, dentine, cementum or combinations thereof.

Most odontogenic tumours (75%) are odontomas and benign. The second most common is ameloblastoma (12%), which is locally aggressive – followed by odontogenic myxoma, adenomatoid odontogenic tumour, ameloblastic fibro-odontoma, ameloblastic fibroma, calcifying odontogenic cyst and odontogenic fibroma.

Altered expression of platelet-derived endothelial cell growth factor/thymidine phosphorylase (PD-ECGF/TP) and of angiopoietins in ameloblastic tumours may be responsible for aggressive behaviour.

Classification

Tumours of the dental tissues are classified according to the World Health Organization (1992) revised in 2005, mainly related to the tissues of origin and histopathological features. The following main changes were proposed in 2005:

1. odontogenic tumours are not only 'related to' odontogenic tissues but are derived from these;
2. the stroma of the epithelial tumour group is of a fibrous nature and does not contain any ectomesenchymal component;
3. subtypes of ameloblastomas have to be differentiated (intra-, extraosseous, desmoplastic, unicystic);
4. eponyms are no longer used in the revised classification;
5. the AOT is reclassified as an epithelial odontogenic tumour;
6. a neoplastic and non-neoplastic line of the ameloblastic fibroma and ameloblastic fibrodentinoma is proposed;
7. the calcifying ghost cell odontogenic tumour is included in the classification;
8. the simple and the WHO type of odontogenic fibroma are included in the classification;
9. ameloblastic carcinoma is differentiated from malignant (metastasizing) ameloblastoma;

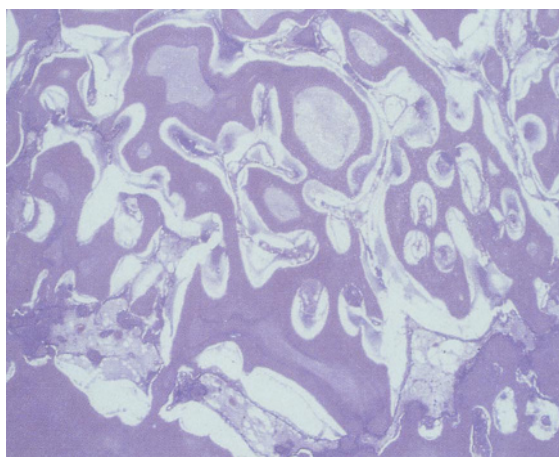


Fig. 33.5 Odontome

10. the term carcinoma in intraosseous (peripheral) ameloblastoma is introduced. Also, the malignant epithelial odontogenic ghost cell tumour is termed calcifying ghost cell odontogenic carcinoma;
11. the clear cell odontogenic tumour is termed clear cell odontogenic carcinoma;
12. the so-called pseudocysts are termed 'cavities' (aneurysmal bone cavity, simple bone cavity, lingual and buccal mandibular bone cavity, focal marrow-containing jaw cavity).

Odontomes

Odontomes are calcified hamartomatous malformations of dental hard tissues and consist of dental tissues in normal relationship one to another (Fig. 33.5). Odontomes have been classified according to the type and spatial arrangement of the dental tissues as follows:

- Odontoma, compound type (compound composite odontomes) – consist of multiple small simple denticles embedded in fibrous connective tissue within a fibrous capsule. Multiple lesions may be seen in Gardner syndrome.
- Odontoma, complex type (complex composite odontomes) – consist of an irregular mass of all the dental tissues.

Clinical features

Odontomes typically present in children and adolescents, are more common in females than males, and show a distinct predilection for the premolar-molar region of the mandible. Typically, they behave like teeth: they grow to a certain size and then tend to erupt with ulceration of the overlying oral mucosa. Alternatively, they may go unnoticed or, if located

over the crown of an unerupted tooth, may prevent eruption. They may displace adjacent teeth or impede eruption.

Diagnosis

Radiographically, the lesions appear as small well-defined radio-opacities.

Management

The lesions should be excised, but considerable mechanical difficulty may be encountered.

Enamel pearls

Rarely, disturbances in odontogenesis cause small deposits of enamel, termed enamel pearls (enamelomas), usually between the roots of the first permanent molars. No treatment is required.

Dentinoma

Focal deposits of dentine or osteodentine have been found overlying the crown of unerupted mandibular molar teeth in young adults and have been termed 'dentinomas'. The lesions are usually asymptomatic and appear as chance findings, as opacities on radiographic examination.

Cementoma

Cementum is normally deposited on tooth roots throughout life to compensate for occlusal wear; an excess of such physiological deposition is termed 'hypercementosis'. The common causes of hypercementosis are chronic periapical infection, a functionless tooth, a reaction to increased stress on the tooth, and Paget's disease. Hypercementosis is often symptomless and causes complications only during exodontia.

Alternatively, cementum may be deposited neoplastically, when the lesion is termed a 'cementoma' – uncommon lesions, which include:

- benign cementoblastoma
- gigantiform cementoma
- periapical cemental dysplasia
- cementifying fibroma.

Dens invaginatus

Dens invaginatus arises because, during odontogenesis, a portion of the enamel organ protrudes, or invaginates, into the dental papilla. Thus, when development has

been completed, the affected and distorted tooth (dilated odontome) contains a cavity that is completely or partially lined by enamel, radiographically resembling a tooth within a tooth (dens in dente). Dens invaginatus occurs in children and adolescents, shows no sex predilection, commonly affects the permanent dentition, usually the upper lateral incisor or an upper anterior tooth, and not infrequently is bilateral. The degree of invagination may be mild to severe, presents as a small pit on the palatal surface of the affected tooth, and the defect collects plaque and food debris, as a result of which there is often caries and consequently pulpitis and periapical infection.

Routine conservation is adequate for mild defects but, in more severe cases, particularly where there is pulpitis or periapical infection, extraction is needed.

Dens evaginatus (talon cusp)

In this instance, an evagination causes a nodule usually on the occlusal surface of mandibular premolars, but may be seen buccally or lingually on other teeth. It is most common in Mongoloid races.

Geminated odontome

A geminated odontome is a large abnormal tooth that is actually composed of two joined teeth, resulting either from partial division of a tooth germ, or from the fusion of adjacent tooth germs. Gemination is seen mainly anteriorly; the crowns may be separate or divided by a groove. Similarly, the roots may be fused or separate.

Ameloblastoma (adamantinoma)

The ameloblastoma is the most common odontogenic neoplasm. It is a locally invasive lesion arising from the dental lamina, Hertwig sheath, the enamel organ, or the lining of dental follicles/dentigerous cysts. Fos (a transcription factor) and TNFRSF (tumour necrosis factor receptor super family) genes are overexpressed.

Clinical features and diagnosis

Ameloblastomas are more frequent in males, and usually appear after the age of 40 years. Unicystic variants occur in adolescence. Some 80% are found in the mandible, most in the posterior mandible. The tumour is not uncommon in people of African heritage compared to the lower incidence in white people.

The initial detection of an ameloblastoma is likely to be a 'chance finding', but, when the tumour is evident clinically, there is a slow-growing, painless, expansile swelling of bone. The lesion expands to produce progressive

facial deformity and intraorally there may be evidence of malocclusion and mobile teeth. Eventually the bone is perforated and soft tissues involved.

Diagnosis

A monocystic (unicystic) or polycystic ('soap bubble') radiolucency is evident. Diagnosis is confirmed by histological examination of a biopsy specimen. Ameloblastomas are composed of epithelial cells arranged as a peripheral layer of ameloblast-like cells around a central area of cells resembling stellate reticulum (Fig. 33.6). Two main histological types are seen: follicular and plexiform types. In the follicular type, discrete islands (follicles) of epithelial cells are evident, whereas in the plexiform type the epithelium forms continuous anastomosing strands. Enamel formation is not evident, presumably because no odontogenic mesenchyme is present to give the critical inductive forces.

Histological variations occasionally seen include granular cells, squamous metaplasia and keratinization, areas of calcification and variable degrees of vascularity. However, there appears to be little correlation between these histological patterns and the clinical course of the tumour. Features such as increased cellular pleomorphism and mitotic activity do, however, suggest that the lesions will behave more aggressively.

Management

Despite the ameloblastoma expanding rather than destroying bone, there is also some local invasion of the surrounding bone. The treatment of choice, therefore, is surgical excision of the tumour together with removal of a margin of normal bone and retention of the lower border of the mandible.

Metastatic dissemination is rare and usually occurs by aspiration to the lungs following longstanding local disease or previous surgical intervention.

Odontogenic myxoma (myxoma of the jaws)

Clinical features and diagnosis

Odontogenic myxoma is derived from odontogenic mesenchyme and usually occurs in adolescents and young adults (10–40 years), more frequently in females than males, and usually in the posterior region of the mandible. The maxillary lesions that have been reported are characterized frequently by extensive involvement of the alveolar bone, the antrum and the zygomatic process. Clinically, the myxoma is an intrabony lesion that slowly expands the bony cortex

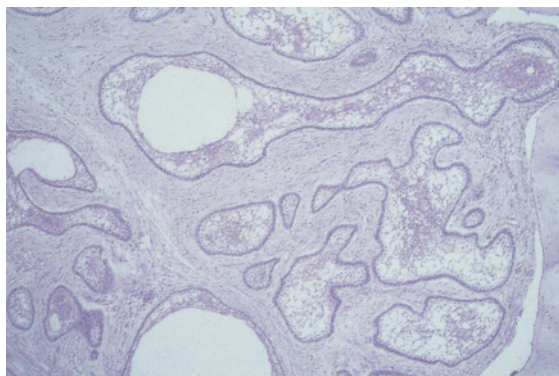


Fig. 33.6 Ameloblastoma

and only perforates later. The lesion is rarely painful, but there may be loosening and displacement of the teeth.

Radiographic examination shows a well-defined unilocular or multilocular ('soap bubble') radiolucency, which may extend between the roots of the teeth and, thus, a scalloped margin is seen. On microscopic examination of biopsy specimens, spindle/stellate shaped cells are present in an intercellular mucoid stroma, sometimes containing nests of epithelial cells. Fibrous tissue and collagen are frequently evident throughout the lesion ('fibromyxoma'). There is widespread infiltration of the surrounding bone.

Management

Myxomas infiltrate and, therefore, should be treated with surgical excision of the tumour and removal of a margin of normal bone.

Adenomatoid odontogenic tumour (AOT: adenoameloblastoma)

AOT is an uncommon and benign tumour.

Clinical features and diagnosis

The AOT may be remembered as the 'two-thirds tumour' since:

- it most commonly occurs in the second and third decades of life
- two-thirds of cases are seen in females
- two-thirds of cases occur in the anterior maxilla
- two-thirds of the cases are associated with an impacted tooth (usually the canine).

Clinically, the lesion presents as a gradually increasing intrabony swelling, which is occasionally painful.

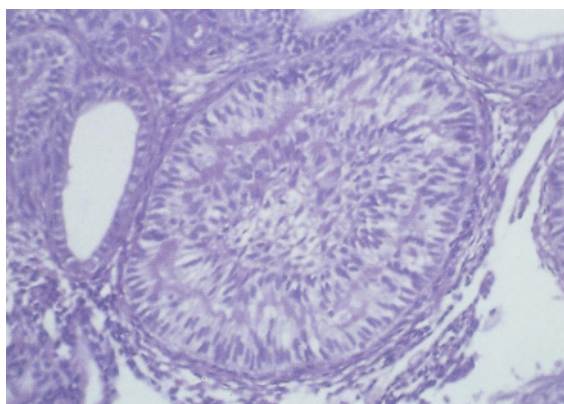


Fig. 33.7 Adenomatoid odontogenic tumour

On radiographs, the tumour appears as a unilocular radiolucency sometimes with radio-opaque foci. A clinical provisional diagnosis should include either a lateral periodontal cyst or a dentigerous cyst, particularly as, in the latter case, the tumour is sometimes associated with an unerupted tooth.

On histological examination, the tumour is encapsulated and consists of sheets and strands of epithelial cells arranged as convoluted bands and tubular structures (Fig. 33.7). In the tubular structures, ameloblast-like cells are arranged radially around spaces containing a homogeneous eosinophilic material. The nature of this material is unknown, although suggestions have included pre-enamel, pre-dentine, amyloid and basement membrane material. Separate from the homogeneous material, foci of calcification frequently are evident throughout the lesion. The tumour contains little intervening mesenchymal stroma, although cystic degeneration of this tissue is common.

Management

The AOT is not locally invasive and does not recur following conservative surgical excision.

Calcifying epithelial odontogenic tumour (CEOT; Pindborg tumour)

Clinical features and diagnosis

CEOT is rare, benign, but aggressive, and has been reported in all age groups (10–90 years), but manifests most commonly as a progressive painless swelling of the jaws at approximately 40 years of age. It has no gender predilection and is most frequent in the mandibular premolar-molar region. It is associated with an unerupted or impacted tooth in 50% of cases. Rarely, it is extraosseous in more anterior parts of the mouth.

Radiographically, the tumour usually appears as a radiolucency containing focal opacities. Histological examination shows three distinct features:

- Sheets of epithelial cells (containing tonofilaments, desmosomes and hemi-desmosomes), which are pleomorphic and contain abnormal nuclei. In places, these cells are characterized by a clear cytoplasm, and hence have been termed 'clear cells'. Mitoses are rare.
- Amyloid, with its characteristic staining (green birefringence with Congo red stain; positive fluorescence with thioflavine T).
- Concentric masses of calcified tissues – often closely associated with the epithelial cells.

Management

The CEOT is locally invasive and, therefore, treated with surgical excision plus a margin of normal bone.

Calcifying epithelial odontogenic cyst

Clinical features and diagnosis

Calcifying epithelial odontogenic cyst is extremely rare, and most commonly presents in adults younger than 40 years. Either jaw of either sex may be affected, but most are anterior to the first molar.

Clinically, there is a slowly enlarging, painless swelling of the jaws, which, on radiographic examination, commonly appears as a well-defined unilocular or multilocular radiolucency containing flecks of opacity. Embedded teeth and/or denticle-like structures are not infrequent findings.

Microscopically, the tumour may be solid or cystic. In cystic lesions, the cyst wall is lined by odontogenic epithelium resembling that in an ameloblastoma, with peripheral ameloblast-like cells in close association with more central cells comparable to the stratum intermedium and the stellate reticulum. In places, the epithelial cells undergo aberrant keratinization to form large eosinophilic cells without a nucleus, termed 'ghost cells'. With further development, large masses of keratin accumulate and a foreign body giant cell reaction may be evoked if there is breakdown of the epithelial cyst lining. Foci of calcification and dentine-like material frequently are present throughout the specimen.

Management

Conservative enucleation is usually adequate.

The keratinizing and calcifying odontogenic cyst (KCOC or Gorlin cyst)

Clinical features and diagnosis

KCOC is a neoplasm with cystic tendencies arising from a more mature enamel epithelium than does the ameloblastoma and, accordingly, has less growth potential. KCOC has no age, sex, or location predilections and may be found anywhere in the jaws. Up to one-fourth of lesions are found in peripheral soft tissues (e.g. gingiva). They appear as nondescript radiolucencies that may contain flecks of opacity. The lesions are lined by an epithelium that is similar in appearance to ameloblastoma, but the cells have no nuclei and are called ghost cells (ghost epithelium) – which eventually herniate into the connective tissue, causing a connective tissue foreign body response that results in dentinoid dystrophic calcification and the formation of granulation tissue.

Management

These lesions are surgically removed and rarely recur.

Odontogenic fibroma

Odontogenic fibroma is a rare tumour that may be peripheral or central. The tumour generally presents in close relation to the root of a tooth, the crown of an unerupted tooth, or in the site of a tooth that is congenitally missing. Histologically, the lesion consists of fibrous tissue which has a similar appearance to the dental pulp, but contains small nests of odontogenic epithelium.

Conservative enucleation is the treatment of choice.

Ameloblastic fibroma

Clinical features and diagnosis

Ameloblastic fibroma is a tumour that occurs in young adults (15–25 years) presenting as a slow, painless jaw expansion and appears as a unilocular radiolucency. Infrequently, the tumour may be associated with an unerupted tooth.

Histologically, odontogenic epithelium is present as small islands, elongated strands, or terminal buds of peripheral ameloblast-like cells and central stellate reticulum cells. The odontogenic mesenchyme resembles the dental papilla. Surrounding the epithelial component there is frequently a cellular hyaline material thought to be the product of epithelial-mesenchymal interaction.

Uncommonly, dentine or dentinoid may be present, and this has led to the term ‘ameloblastic fibro-dentinoma’ being used. In some instances young enamel may also be found in close relationship with the dentinoid, and these tumours are known as ameloblastic fibro-odontomas.

Management

Management is by conservative enucleation.

Ameloblastic fibro-sarcoma

Malignant counterparts of the ameloblastic fibroma are very rare. The lesions are preceded by pain and are characterized by a rapid enlargement of the jaw. Biopsy shows an odontogenic epithelial component similar to that found in an ameloblastic fibroma, whereas the mesenchymal tissues resemble a fibrosarcoma with cellular pleomorphism, tumour giant cells and numerous, atypical mitotic figures. Variations in which dentinoid are found are known as ameloblastic fibro-dentinomas and if there is also rudimentary enameloid present, these have been called ameloblastic fibro-odontosarcomas.

Treatment involves radical surgery.

Further reading

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34 Pemphigoid

Key points

- Mucous membrane pemphigoid (MMP) is a chronic autoimmune disease affecting mucous membranes and/or skin.
- The autoantibodies are directed against epithelial basement membrane zone (BMZ) proteins, especially integrin and epiligrin.
- Immune deposits result in a subepithelial split and blistering.
- Oral lesions include bullae and erosions and desquamative gingivitis.
- Diagnosis is achieved by biopsy with immunostaining
- Treatment is with corticosteroids or dapsone.

Introduction

Autoimmune blistering mucocutaneous diseases can be divided into two major subsets:

- the pemphigoid subset – mediated by autoantibodies that target the extracellular components that link the epithelial basement membrane components either to the lowermost layer of epithelial cells or to the lamina propria components (subepithelial blistering, or immune-mediated subepithelial blistering diseases – IMSEBD). This region, the epithelial basement membrane zone (BMZ), has a highly complex structure composed of an array of proteins. Autoantibodies directed against these proteins can produce a range of disorders (Figs 34.1 and 34.2), but all show immune deposits at the BMZ and subepithelial splitting of epithelium from the lamina propria and all can be clinically similar. Special immune studies are required to separate these similar phenotypes.
- the pemphigus subset – mediated by autoantibodies that target the extracellular components that link one epithelial cell to another (intra-epithelial blistering) (see Ch. 35).

Pemphigoid is the term given to a group of subepithelial immunologically mediated vesiculobullous disorders that can affect stratified squamous epithelium. It is characterized by damage to one of the protein constituents of the basement membrane zone (BMZ) anchoring filament components. A number of other subepithelial vesiculobullous disorders may produce

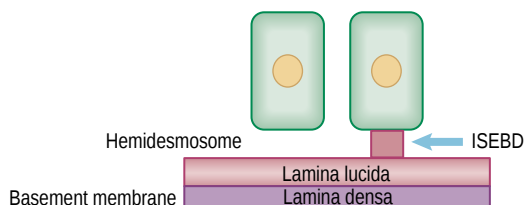


Fig. 34.1 Immune mediated subepithelial blistering diseases – lesion at BMZ

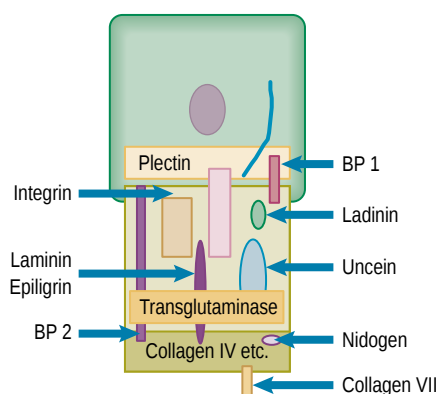


Fig. 34.2 Complexity of hemidesmosome and epithelial basement membrane zone. BP, bullous pemphigoid

Box 34.1

Subepithelial vesiculobullous disorders

- Pemphigoid variants
- Dermatitis herpetiformis
- Acquired epidermolysis bullosa
- Toxic epidermal necrolysis
- Erythema multiforme
- Dermatitis herpetiformis
- Linear IgA disease
- Chronic bullous dermatosis of childhood

similar clinical features (Box 34.1). The main types of pemphigoid that involve the mouth are termed 'oral' or 'mucous membrane pemphigoid' (MMP) and include the following:

- Mucous membrane pemphigoid, in which mucosal lesions predominate, but skin lesions are rare. MMP is sometimes termed 'cicatricial pemphigoid' (CP).

- Oral mucosal pemphigoid, which occurs in patients with oral lesions only. This lesion does not involve a progressive ocular scarring process and is without serologic reactivity to bullous pemphigoid antigens.
- Bullous pemphigoid, which affects mainly the skin.
- Ocular pemphigoid, which affects mainly the conjunctivae and may cause scarring.

However, most of the literature has failed to distinguish mucous membrane from oral pemphigoid, since their distinction has only recently been recognized, and, therefore, the following discussion groups them together.

Mucous membrane/oral pemphigoid

MMP (or sometimes termed 'benign mucous membrane pemphigoid') is a chronic autoimmune disease of the mucous membranes and/or skin.

Incidence

This lesion is not uncommon.

Age

The onset is usually in the fifth to sixth decades.

Sex

Pemphigoid is twice as common in females.

Geographic

There is no known geographic incidence.

Table 34.1
Antigens implicated in subepithelial disorders

Disease	Antigen
Bullous pemphigoid	BP1, BP2*
Mucous membrane pemphigoid	BP2, Laminin 5,† 200 kDa, 168 kDa
Oral pemphigoid	Integrin
Linear IgA disease	97 kDa, 45 kDa
Epidermolysis bullosa acquisita	Type VII collagen
Toxic epidermal necrolysis	105 kDa

*Bullous pemphigoid.

†Also known as epiligrin, nicein, kalinin and BM600.

Predisposing factors

- The precipitating event is unclear in most cases.
- Occasional cases are drug-induced (e.g. by furosemide or penicillamine).
- A genetic predisposition is suggested by HLA associations (with HLA-DQB1*0301, DQB1*0302, 0303 and 06, and especially the DRB1*1101 DQB1*0301 haplotype).

Aetiology and pathogenesis

MMP is an autoimmune type of disorder, characterized immunologically by:

- deposition of immunoglobulins and complement components at the epithelial basement membrane zone (BMZ), suggesting antibodies are directed against the basement membrane
- circulating autoantibodies to basement membrane zone components
- deposits at the epithelial basement membrane zone, which are classically of IgG class (97%) with C3 (78%), but sometimes IgA (27%) or IgM (12%). This further suggests that this is a heterogeneous group of disorders. This has been confirmed and it is evident that a range of variants exist, with antibodies directed against various hemi-desmosomal components or components of the lamina lucida (Table 34.1):
 - the mainly oral variant appears to be associated particularly with anti-integrin antibodies
 - the mainly ocular variant, which also often involves the mouth, appears to be associated especially with anti-epiligrin.

Histologically, MMP is characterized by junctional separation at the level of the epithelial basement membrane zone giving rise to a sub-basilar split as in other forms of pemphigoid (Fig. 34.3). The pathogenesis probably includes complement-mediated sequestration of leukocytes, with resultant cytokine and leukocyte enzyme release and detachment of the basal cells from the BMZ (Fig. 34.4).

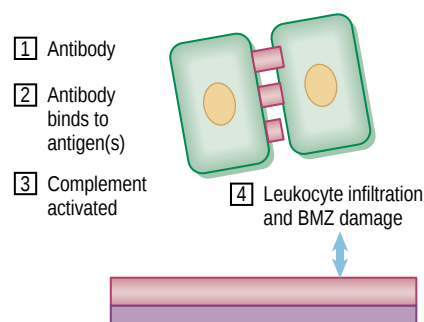


Fig. 34.3 Mucosal pemphigoid pathogenesis

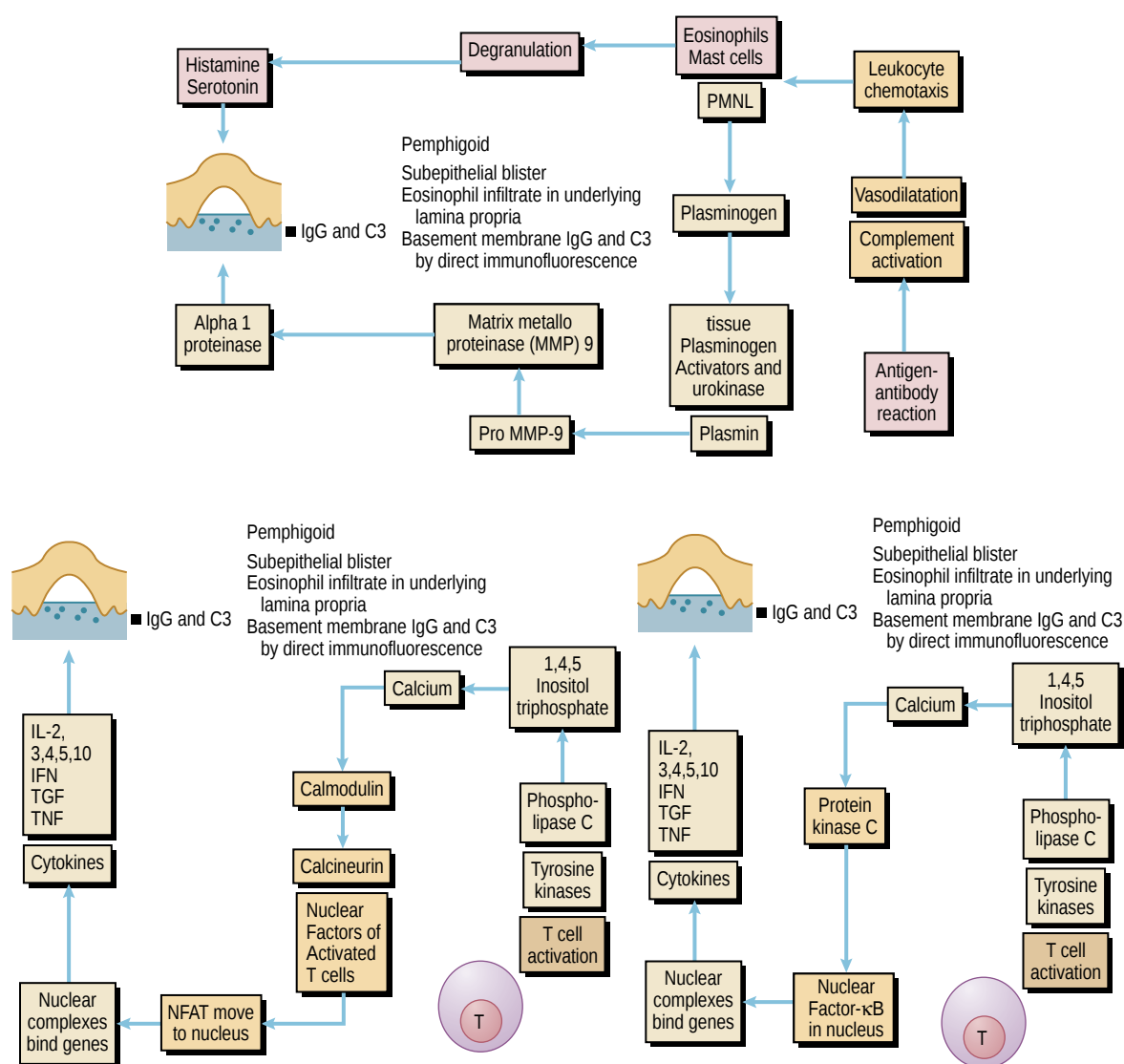


Fig. 34.4 Mucosal pemphigoid pathogenesis

Clinical features

Pemphigoid has a wide clinical spectrum and heals with variable amounts of scar formation. The oral lesions seen in pemphigoid affect especially the gingivae and palate, and may include:

- bullae or vesicles; intact blisters may be seen, but are not common, due to the incidental trauma of eating and speaking (Fig. 34.5). Blisters are tense, may sometimes be blood-filled and can remain intact for several days, similar to those of angina bullosa hemorrhagica (localized oral purpura), often on the soft palate. Pressure on the blister may cause it to spread (Nikolsky sign).

- persistent irregular erosions or ulcers after the blisters burst; these typically are covered with a yellowish fibrinous slough and surrounding inflammatory erythema and, thus, resemble erosive lichen planus, except that no white lesions are present. They may also resemble late lesions of pemphigus.
- scarring, but only rarely in the mouth.
- desquamative gingivitis; this is the most common oral finding and is characterized by erythematous, ulcerated, tender gingiva, usually in a patchy, rather than continuous distribution (Fig. 34.6). Sole involvement of the gingiva is not uncommon and is frequently misdiagnosed as inflammatory periodontal disease.



Fig. 34.5 Mucosal pemphigoid may present with blisters, which break to leave erosions



Fig. 34.6 Mucosal pemphigoid commonly presents with desquamative gingivitis

The majority of affected individuals with MMP have oral involvement only, but:

- untreated ocular involvement can lead to blindness mainly due to conjunctival scarring (leading to entropion, symblepharon or ankyloblepharon) (Fig. 34.7)
- laryngeal scarring may lead to stenosis
- nasal lesions may bleed and crust
- genital involvement can be a source of great morbidity
- skin blisters may rarely be seen
- internal malignancy may be present in some patients with anti-epiligrin pemphigoid.

Diagnosis

The oral lesions of pemphigoid may be confused clinically with pemphigus, angina bullosa haemorrhagica, dermatitis herpetiformis and linear IgA disease or, occasionally, erosive lichen planus, acquired epidermolysis bullosa, toxic epidermal necrolysis or erythema

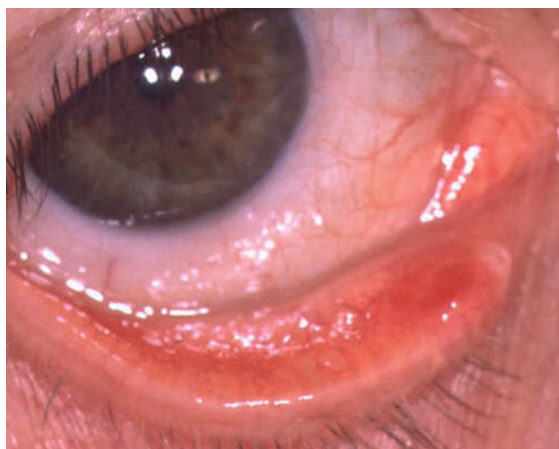


Fig. 34.7 Mucosal pemphigoid may cause ocular disease and scarring

multiforme. Furthermore, the pemphigoid variants are indistinguishable one from another clinically, by light microscopy and conventional immunostaining.

Therefore, biopsy of perilesional tissue, with histological and immunostaining examination can be essential to the diagnosis. The incisional biopsy specimen exhibits subepithelial clefting following staining with haematoxylin and eosin (Fig. 34.8). Direct immunostaining is required to reveal the presence of BMZ immune deposits. Indirect immunofluorescence is frequently negative and the levels of serum antibody, when detected with conventional techniques, are rarely of diagnostic significance:

- Direct immunofluorescence microscopy:
 - Direct immunofluorescence microscopy (DIF) deposits at the epithelial basement membrane zone (Fig. 34.9).
- Indirect immunofluorescence microscopy:
 - Indirect immunofluorescence microscopy (IIF) detects epithelial basement membrane zone-binding autoantibodies.
- Indirect immunofluorescence on salt-split substrate:
 - Indirect immunofluorescence on salt-split substrate (ssIIF) uses epithelial substrates in which the lamina lucida of the basement membrane zone has been split at the middle, leaving the target antigens for the autoantibodies of pemphigoid and epidermolysis bullosa acquisita to the roof and the base of the split substrate, respectively.
 - Using salt-split epithelial substrates, ssIIF detects the circulating autoantibodies from patients with pemphigoid and epidermolysis bullosa acquisita binding respectively to the roof and the base of the substrates, thus distinguishing these two diseases. In mucous membrane pemphigoid, circulating autoantibodies can bind to the roof, base, or both, corresponding to the heterogeneity of the target antigens recognized by these autoantibodies.



Fig. 34.8 Mucosal pemphigoid linear immune deposits at BMZ

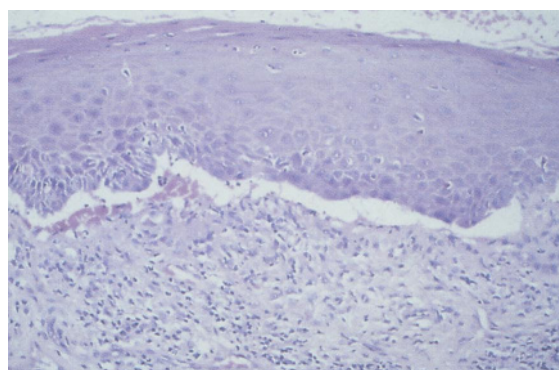
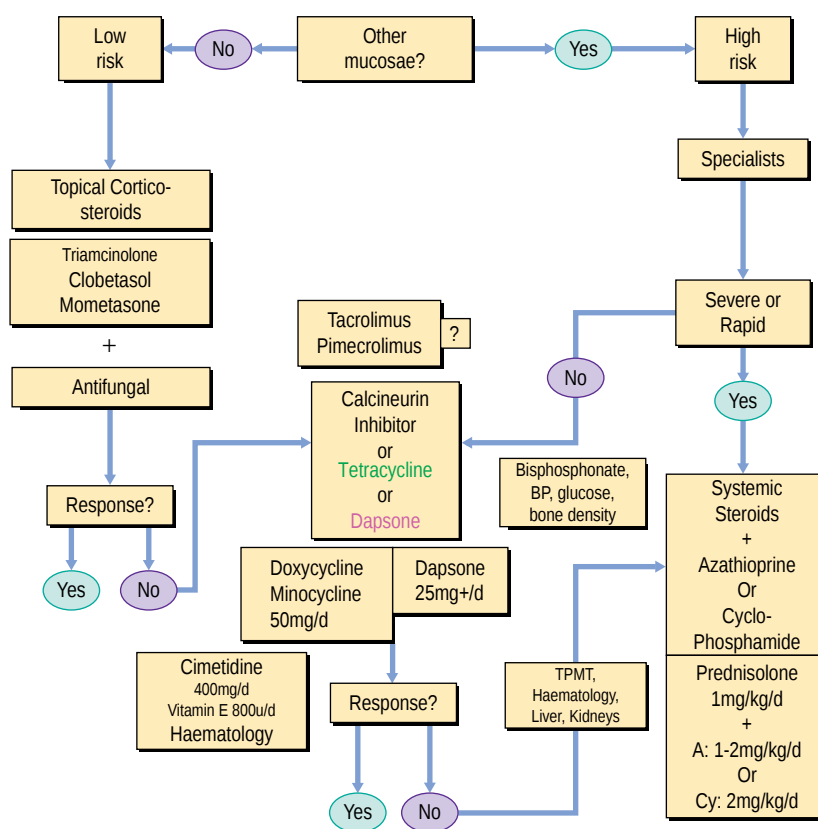


Fig. 34.9 Oral pemphigoid – histopathology showing sub-epithelial split



TPMT= thiopurine methyl transferase

A= azathioprine

Cy= cyclophosphamide

BP= blood pressure

Algorithm 34.1 Management of pemphigoid

Management

Patient information sheet

PEMPHIGOID

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon condition.
- The cause is unknown, but it may be immunological.
- It is not thought to be inherited.
- It is not thought to be infectious.
- It occasionally affects the skin or other sites.
- It usually has no long-term consequences.
- Blood tests and biopsy are often required.
- Pemphigoid may be controlled, but rarely cured with medicines.
- Useful website: <http://www.dent.ucla.edu/pic/members/MMP>

Few patients with pemphigoid have spontaneous remission and, thus, treatment is often indicated ([Algorithm 34.1](#)):

- Systemic manifestations must be given attention. Ocular manifestations have been reported in up to 20% of patients and, left untreated, can lead to blindness and thus an ophthalmological consultation is essential. Patients with MMP should also be questioned about the presence of other mucosal symptoms, which might indicate genital involvement. Patient information is an important aspect in management.
- The majority of cases respond well to topical corticosteroids or tacrolimus, which are also the usual treatment for desquamative gingivitis and may be effective if used in a vacuum-formed custom tray or veneer worn during sleep.
- The management of desquamative gingivitis associated with pemphigoid should also include oral hygiene improvement, as secondary infection may inhibit healing.

- Severe pemphigoid may need to be treated with dapsone or immunosuppression using azathioprine or systemic corticosteroids, but this is of variable benefit and/or can give rise to serious adverse effects.

Websites

<http://www.aarda.org/indexf.html>

Further reading

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35 Pemphigus

Key points

- Pemphigus is a group of potentially life-threatening chronic autoimmune diseases characterized by epithelial blistering affecting mucocutaneous surfaces.
- Autoantibodies in pemphigus vulgaris are directed against desmoglein in epithelial desmosomes.
- Immune deposits result in intra-epithelial splitting (acantholysis).
- Epithelial blistering and erosions often manifest first in the mouth.
- Diagnosis is confirmed by biopsy and immunostaining.
- Treatment necessitates systemic immunosuppressants.

Introduction

Pemphigus is the term for a group of potentially life-threatening chronic autoimmune diseases characterized by epithelial blistering affecting mucocutaneous surfaces, the term being derived from the Greek *pemphix* (bubble or blister). Autoantibodies are directed against desmosomes – structures that bind stratified squamous epithelial cells together and that have a complex protein structure (Fig. 35.1).

There are several variants of pemphigus due to autoantibodies directed against the different desmosome constituents (especially desmogleins) and, since the resultant damage is at different levels within the epithelium, clinical manifestations may vary somewhat (Fig. 35.2). The main types are:

- pemphigus vulgaris: this includes an uncommon variant – pemphigus vegetans. The main antigen in pemphigus vulgaris is desmoglein (Dsg) 3, a constituent of oral epithelial intercellular cement. Oral lesions are invariable.
- pemphigus foliaceus: this includes the uncommon variant pemphigus erythematosus (Senear–Usher syndrome). The main antigen in pemphigus foliaceus is Dsg 1, a constituent mainly of skin epithelium. Oral lesions are rare.

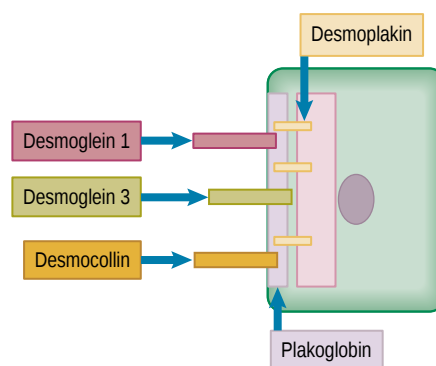


Fig. 35.1 Desmosomal proteins

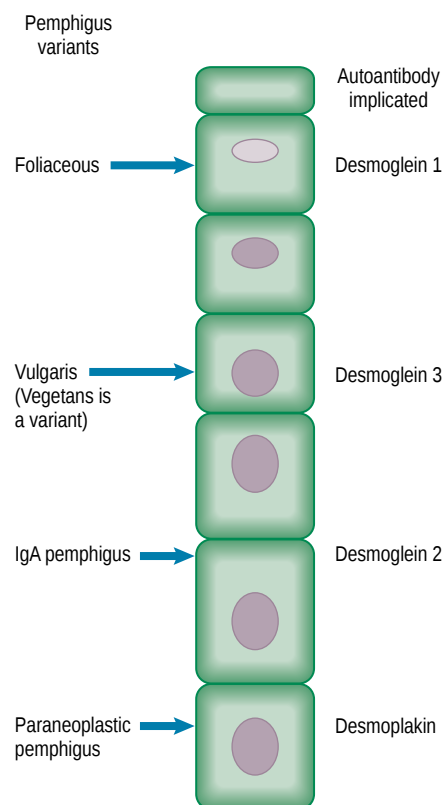


Fig. 35.2 Pemphigus variants and antigens autoantibodies implicated

Pemphigus vulgaris is the most common pemphigus variant, and the form responsible for most oral lesions.

Pemphigus vulgaris

Incidence

Pemphigus vulgaris is a rare disease.

Age

Pemphigus vulgaris is found mainly in middle-aged and elderly patients.

Sex

There is a female predisposition.

Geographic

Pemphigus vulgaris predominately occurs in middle-aged patients of Ashkenazi Jewish, Asian or Mediterranean descent.

Predisposing factors

- There is a fairly strong genetic background to pemphigus vulgaris, and an HLA association with DRB1*0402, 1401 and DQB1*0302, 1503.
- Most cases are idiopathic, but some have been triggered by:
 - medications (captopril and penicillamine, which contain sulphhydryl groups, and rifampicin and diclofenac)
 - radiation
 - surgery
 - certain foods, such as garlic
 - emotional stress.

Aetiology and pathogenesis

- Serum antibodies, mainly IgG (particularly IgG4 class) are directed predominantly against desmosomes in stratified squamous epithelia. Intercellular immune deposits (mainly IgG and C3), are detectable intraepithelially (Fig. 35.3).
- The antigen-antibody response on epithelial surfaces activates plasminogen to plasmin, leading to damage to desmosomal cadherin-type epithelial cell adhesion molecules, particularly Dsg 3 and plakoglobin. This causes loss of cell-cell contact (acantholysis), and thus intraepithelial vesiculation (Figs 35.4 and 35.5).

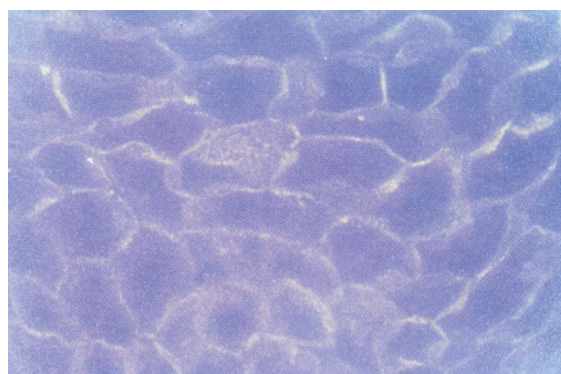


Fig. 35.3 Immunofluorescence in pemphigus showing intercellular antibodies

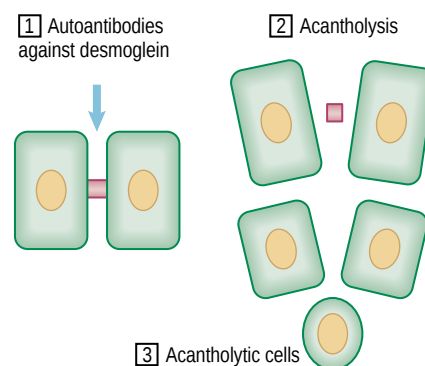


Fig. 35.4 Pathogenesis of pemphigus

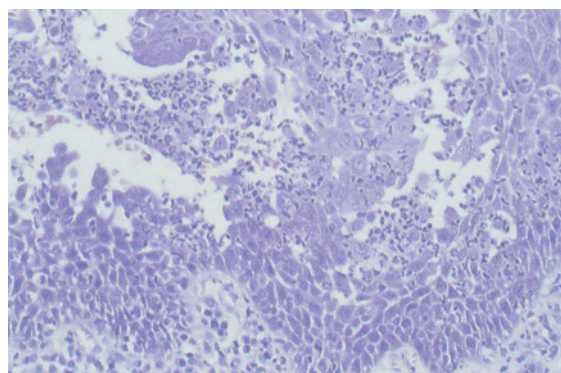


Fig. 35.5 Histopathology showing acantholysis in pemphigus

- Since oral epithelium expresses largely Dsg 3, but skin expresses Dsg 1 as well as Dsg 3, damage by antibodies against Dsg 3 results in oral lesions at an early stage, whereas skin integrity is maintained by Dsg 1. However, if Dsg 1 antibodies appear, cutaneous lesions result and the disease tends to be more severe (Table 35.1).
- Other autoimmune diseases, such as myasthenia gravis and systemic lupus erythematosus, are occasionally associated.

Table 35.1
Antibodies to desmogleins in pemphigus vulgaris

Pemphigus vulgaris lesions	Dsg 3	Dsg 1
Mucosal mainly	+	–
Mucocutaneous	+	+

Clinical features

Pemphigus vulgaris is the most severe form of pemphigus, and typically runs a chronic course, causing blisters and scabs on the skin and also blisters, erosions and ulcers on the mucosae of the:

- mouth
- pharynx
- larynx
- oesophagus
- rectum
- nose
- conjunctiva
- anogenital region.

Pemphigus vulgaris often begins with blister formations (bullae) occurring in the mouth and on the scalp. The blisters are soft and are easily broken. The Nikolsky sign (the spreading of a blister by pressure) is positive.

Oral lesions in pemphigus vulgaris:

- are common
- may be an early manifestation
- may be the sole manifestation for a considerable time
- are vesiculobullous, but readily rupture, new bullae developing as the older ones rupture and ulcerate
- form erosions, which are irregular and initially red with a whitish surround (Fig. 35.6), but later are yellowish as a slough forms (Fig. 35.7)
- are seen mainly on the:
 - soft palate and posterior hard palate
 - buccal mucosa
 - lips
 - gingiva, where lesions usually comprise severe desquamative or erosive gingivitis; flaps of peeling tissue with red erosions or deep ulcerative craters are seen, mainly on the attached gingivae
- are almost invariably followed by involvement of the skin or, occasionally, other epithelia, such as the oesophagus, in the absence of systemic treatment.

Diagnosis

- Diagnosis of an autoimmune bullous disease should be suspected when there is no clear history of exposure to a drug or allergen or when other studies for infectious origins, such as herpes or impetigo, are negative.



Fig. 35.6 Pemphigus; early red oral lesions



Fig. 35.7 Pemphigus; lesions become erosions with a yellowish slough

- The differential diagnosis often includes:
 - pemphigoid
 - erythema multiforme and toxic epidermal necrolysis
 - pyostomatitis vegetans
 - paraneoplastic pemphigus
 - IgA pemphigus (intraepithelial IgA pustulosis)
 - pemphigus associated with inflammatory bowel disease.
- other types of pemphigus, such as pemphigus foliaceus and erythematosus and pemphigus vegetans, which only rarely affect the oral mucosae.
- To differentiate these bullous diseases, a careful history and physical examination are important, but biopsy is mandatory.
- Biopsy of perilesional tissue, with histological and immunostaining examination are essential.
- Serum should be collected for titres of antibody to epithelial intercellular cement, which may help guide treatment. Serum autoantibodies to Dsg are best detected using both normal human skin and

Table 35.2**Monitoring protocol for patients with pemphigus on systemic corticosteroid therapy during the first 3 months of therapy***

Daily	Weekly	Monthly
Diet low in sodium and carbohydrate	Clinical oral examination	Titre of serum antiepithelial antibodies
Blood pressure estimation	Body weight estimation	-
Recording of symptomatology	Recording of symptomatology	Haematological examination for first month, then every 15–30 days

*Bone densitometry every 6 months.

monkey oesophagus by enzyme-linked immunosorbent assay.

- Direct immunofluorescence microscopy:
 - Direct immunofluorescence microscopy (DIF) detects deposits at the epithelial cell surfaces. In paraneoplastic pemphigus, DIF usually reveals deposits at both the epithelial cell surfaces and the epithelial basement membrane zone.
- Indirect immunofluorescence microscopy:
 - Indirect immunofluorescence microscopy (IIF) detects epithelial cell surface-binding autoantibodies. The titre of circulating autoantibodies corresponds to the severity of disease in pemphigus.
 - In addition to binding to squamous epithelial cell surfaces (e.g. skin, oesophagus substrates), circulating autoantibodies from patients with paraneoplastic pemphigus also label transitional epithelium (e.g. rat bladder).

Patient information sheet

PEMPHIGUS

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a rare condition.
- It is an immunological disease, the immune reaction damaging the skin.
- It is most commonly seen in persons from around the Mediterranean.
- It is not usually inherited.
- Pemphigus is not known to be infectious.
- It affects the mouth, skin and other sites.
- Uncontrolled it is a very dangerous condition.
- Blood tests and biopsy are usually required.
- Strong drugs such as steroids are normally needed to control pemphigus.
- Useful website: <http://www.pemphigus.org>
- Advice is available from:
 - Pemphigus Vulgaris Network, Flat C, 26 St. German's Road, London SE23 1RJ
 - National Pemphigus Vulgaris Foundation, PO Box 9606, Berkeley, CA 94709-0606, USA. Tel. (+1) 510 527 4970.

Management

Before the introduction of corticosteroids, pemphigus vulgaris typically was fatal mainly from dehydration or secondary systemic infections. Pemphigus vulgaris remains a life-threatening disorder, though current treatment, largely based on systemic immunosuppression, has significantly reduced the mortality to about 10%. Physician involvement and patient information are, thus, important.

Patients with severe oral lesions should be referred to a:

- pulmonary specialist, especially those patients with paraneoplastic pemphigus, and particularly if the patients have symptoms or signs suggestive of respiratory difficulty
- gastroenterologist – to detect possible oesophageal involvement.

Systemic therapy, often with corticosteroids (e.g. prednisolone at least 60 mg/day) is essential, unless there are only localized oral lesions, when topical corticosteroids or intralesional corticosteroids may suffice for a time (Table 35.2). Once under control, the dosage of prednisolone can be tapered or adjuncts added. Adjuncts or alternatives include:

- azathioprine
- ciclosporin
- cyclophosphamide
- others, such as gold, dapsone, chlorambucil, levamisole and immunoglobulins.

It is possible to eventually induce complete and durable remissions in most patients, permitting systemic therapy to be safely discontinued without a flare in disease activity. The proportion of patients in whom this can be achieved increases steadily with time, and therapy can be discontinued in approximately 75% of patients after 10 years. Oral lesions are persistent, and are often recalcitrant even when cutaneous lesions are controlled by treatment.

Websites

American Autoimmune Related Diseases Association: <http://www.aarda.org>
 National Pemphigus Foundation: <http://www.pemphigus.org>

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36

Salivary neoplasms

Key points

A wide range of different uncommon neoplasms can affect the salivary glands, but most are epithelial neoplasms, present as unilateral swelling of the parotid and are benign. The 'rule of nines' is an approximation that states that 9 out of 10 salivary gland tumours:

- affect the parotid
- are benign
- are pleomorphic salivary adenomas (PSAs).

Introduction

A wide range of different uncommon neoplasms can affect the salivary glands, but most are epithelial neoplasms, present as unilateral swelling of the parotid and are benign (Fig. 34.1). The 'rule of nines' is an approximation that states that 9 out of 10 salivary gland tumours:

- affect the parotid
- are benign
- are pleomorphic salivary adenomas (PSAs).

The next most common is carcinoma. Other neoplasms of major salivary gland are usually monomorphic adenomas (such as adenolymphomas), mucoepidermoid tumours or acinic cell tumours.

The World Health Organization classification is the most widely used classification of salivary gland neoplasms (Box 36.1). The epithelial tumours, which are the most important, can be memorized by the mnemonic 'A Most Acceptable Classification':

- Adenomas
- Mucoepidermoid tumour – intermediate (see below)
- Acinic cell tumour – intermediate (see below)
- Carcinomas and other neoplasms.

Incidence

These are uncommon neoplasms.

Age

Most salivary gland neoplasms are seen in older people.

Sex

There is a female predisposition to salivary gland neoplasms.

Geographic

Salivary gland tumours are more common in certain geographical locations. Inuits, for example, have an increased prevalence.

Predisposing factors

There is a correlation between salivary gland and breast cancer.

Aetiology

The aetiology is unknown, but salivary gland tumours have been associated with:

- Epstein-Barr virus infection, at least in Asian patients and Inuits
- occupation – rubber manufacturing, plumbing industry, woodworking, hairdressing, asbestos exposure
- ionizing radiation exposure, as in:
 - survivors of the atomic explosions in Japan (mucoepidermoid carcinomas and Warthin tumour)
 - the use of iodine-131 in the treatment of thyroid disease
 - radiotherapy to the head and neck
 - radiographs to the head and neck
 - exposure to ultraviolet radiation.

► Box 36.1

WHO classification of salivary gland tumours*

Malignant epithelial tumours

• Acinic cell carcinoma	8550/3
• Mucoepidermoid carcinoma	8430/3
• Adenoid cystic carcinoma	8200/3
• Polymorphous low-grade adenocarcinoma	8525/3
• Epithelial-myoepithelial carcinoma	8562/3
• Clear cell carcinoma, not otherwise specified	8310/3
• Basal cell adenocarcinoma	8147/3
• Sebaceous carcinoma	8410/3
• Sebaceous lymphadenocarcinoma	8410/3
• Cystadenocarcinoma	8440/3
• Low-grade cribriform cystadenocarcinoma	
• Mucinous adenocarcinoma	8480/3
• Oncocytic carcinoma	8290/3
• Salivary duct carcinoma	8500/3
• Adenocarcinoma, not otherwise specified	8140/3
• Myoepithelial carcinoma	8982/3
• Carcinoma ex pleomorphic adenoma	8941/3
• Carcinosarcoma	8980/3
• Metastasizing pleomorphic adenoma	8940/1
• Squamous cell carcinoma	8070/3
• Small cell carcinoma	8041/3
• Large cell carcinoma	8012/3
• Lymphoepithelial carcinoma	8082/3
• Sialoblastoma	8974/1

Benign epithelial tumours

• Pleomorphic adenoma	8940/0
• Myoepithelioma	8982/0
• Basal cell adenoma	8147/0
• Warthin tumour	8561/0
• Oncocytoma	8290/0
• Canalicular adenoma	8149/0
• Sebaceous adenoma	8410/0
• Lymphadenoma:	
• sebaceous	8410/0
• non-sebaceous	8410/0
• Ductal papillomas:	
• inverted ductal papilloma	8503/0
• intraductal papilloma	8503/0
• sialadenoma papilliferum	8406/0
• Cystadenoma	8440/0

Soft tissue tumours

• Haemangioma	9120/0
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Haematolymphoid tumours

• Hodgkin lymphoma	
• Diffuse large B-cell lymphoma	9680/3
• Extranodal marginal zone B-cell lymphoma	9699/3

Secondary tumours

*Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (<http://snomed.org>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours and /1 for borderline or uncertain behaviour.



Fig. 36.1 Salivary gland (parotid) neoplasm

Clinical features

The main clinical feature of a neoplasm is salivary gland swelling (Fig. 10.1; see also Fig. 10.4). A history of gradual painless gland enlargement suggests a benign process while rapid growth, pain or facial nerve palsy are ominous and suggest carcinoma.

Clinical examination may reveal an obvious swelling in the case of the parotid outlining the gland anteriorly to the ear, and causing eversion of the ear lobe. However, some tumours are small and the presentation may be of pain only.

Diagnosis

- A swelling, especially if persistent, may be a neoplasm.
- A detailed history and examination are essential.
- The gland affected may be relevant:
 - parotid tumours are largely PSAs
 - submandibular gland tumours are also usually PSAs; malignant neoplasms contribute up to one-third of all submandibular tumours
 - sublingual gland tumours are exceedingly rare, but virtually all are malignant
 - in minor salivary glands, PSAs are again the most common neoplasm, but only account for around 50%, and most of the remainder are malignant tumours, such as carcinomas and adenoid cystic carcinomas. Minor salivary gland tumours most commonly arise

in the palate, but may be seen in the buccal mucosa or upper lip, rarely in the tongue or lower lip.

- Facial palsy suggests a malignant neoplasm.
- The diagnosis can only be firmly established by biopsy. Preoperative needle biopsy has a high tumour detection rate in experienced hands, more if computed tomography (CT) or ultrasound-guided, although some advocate leaving this until perioperatively if malignancy is likely, because tumour cells can be seeded in the needle track.
- Ultrasonography is useful, non-invasive and readily available.
- Sialography may reveal a filling defect or gland displacement, but is a relatively imprecise and non-specific.
- CT or magnetic resonance imaging (MRI) alone, or in conjunction with sialography, are a more sensitive means of tumour detection.
- MRI can be useful to delineate the lesion.

Management

- Early detection carries a good prognosis.
- The treatment of choice is surgical excision; the main hazard is facial nerve damage and palsy.
- Even PSAs require early removal since, in some cases, carcinoma arises.
- Some malignant salivary neoplasms, such as adenoid cystic carcinoma, invade bone and neural tissues preferentially and wide excision is required.
- Radiotherapy is sometimes used as an adjunct for malignant tumours.

Specific neoplasms

The more important neoplasms only are discussed here.

Pleomorphic adenoma (mixed salivary gland tumour)

Pleomorphic adenoma is:

- the most common salivary gland neoplasm
- usually a slow-growing, lobulated, rubbery swelling with normal overlying skin, but a bluish appearance if intraoral
- usually benign. However, it recurs if excision is inadequate (around 3% recur in 5 years). The tumour is poorly encapsulated and parotid adenomas are in intimate relationship with the facial nerve, both of which make complete excision difficult to achieve.

Pleomorphic adenoma appears to originate from ductal epithelium, which proliferates to contribute many

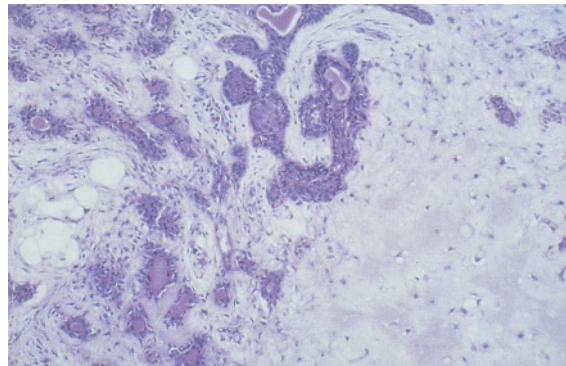


Fig. 36.2 Pleomorphic salivary adenoma

duct-like spaces, sheets of epithelial cells and sometimes areas of squamous metaplasia (Fig. 36.2). There are also areas reminiscent of connective tissue, such as cartilage. The admixture of epithelial elements with what resembles fibrous, myxoid or cartilage tissue, leads to the name 'mixed tumour'. These lesions usually have a thin fibrous capsule, but this is not complete and neoplastic cells may be seen in or outside the capsule. Various genetic abnormalities can be seen – especially involving chromosomes 8 and/or 12, and *PLAG-1* and *HMG1-C* genes.

Malignant change is uncommon, but is suggested clinically by:

- rapid growth
- pain
- fixation to deep tissues
- facial palsy.

Malignant change is shown by obvious malignant features within the benign cellular picture.

Warthin's tumour (papillary cystadenoma lymphomatosum or adenolymphoma)

Warthin's tumour:

- is found virtually only in the parotid
- is found mainly in smokers, in people with autoimmune disease, or those exposed to radiation
- accounts for about 1 in 10 parotid tumours
- is benign
- may be associated with extra-salivary neoplasms.

Columnar cells surround lymphocytes in a folded (papillary) lining to cystic spaces (Fig. 36.3). Chromosome 11q and 19p translocations may be present.

Oncocytoma (oncocytic or oxyphil adenoma)

Oncocytoma:

- is found virtually only in the parotid
- in 20% of cases is in people exposed to radiation

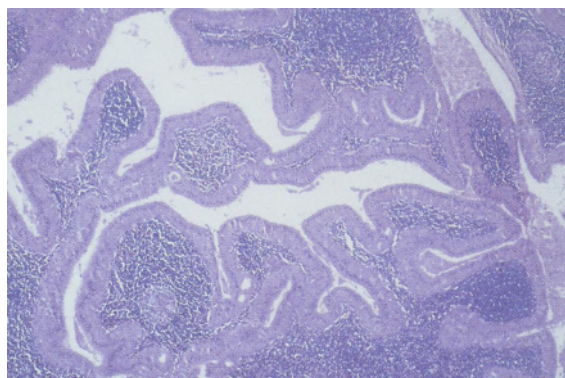


Fig. 36.3 Warthin tumour

- is extremely rare
- affects mainly the elderly
- is benign.

The characteristic of this tumour is that it consists of cords of large eosinophilic cells with small nuclei (oncocytes).

Acinic cell carcinoma

Acinic cell carcinoma:

- is found virtually only in the parotid
- is very rare
- is usually malignant, although all grades of malignancy have been reported.

Acinic cell tumours comprise large cells with a granular basophilic cytoplasm with holes between some cells. The cells resemble serous cells of normal salivary glands.

Mucoepidermoid tumour

Mucoepidermoid tumour:

- accounts for up to 10% of salivary gland tumours
- is slow-growing
- is benign or of low-grade malignancy.

The mucoepidermoid tumour consists of large pale mucus-secreting cells (hence 'muco') surrounded by squamous epithelial cells (hence 'epidermoid') (Fig. 36.4). Chromosome 11q and 19p translocations may be present, with HER-2 gene overexpression.

Adenoid cystic carcinoma

Adenoid cystic carcinoma is:

- slow growing
- malignant, with a tendency to infiltrate, spread perineurally and metastasize.

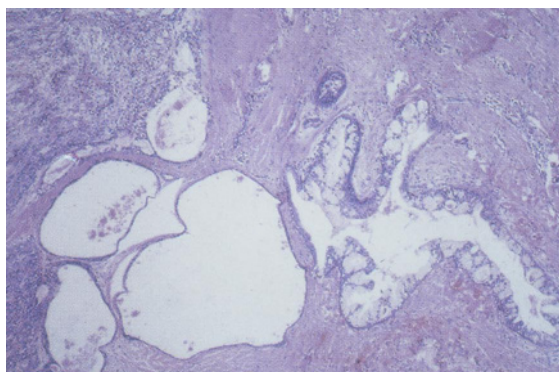


Fig. 36.4 Mucoepidermoid tumour

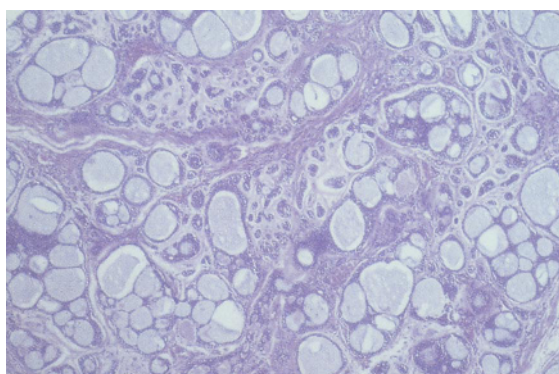


Fig. 36.5 Adenoid cystic carcinoma

Rounded islands of small darkly staining cells surrounding multiple clear areas of varying size (Swiss-cheese appearance) are characteristic (Fig. 36.5). Chromosome 6q, 8q and 12q abnormalities may be present.

Other salivary tumours

- Non-epithelial tumours (e.g. juvenile haemangioma).
- Malignant lymphomas are the next most common neoplasms found in salivary glands. Sjögren syndrome is recognized as predisposing to lymphomas, which have arisen in up to 6% of patients over 10 years in some studies. An intermediate stage between the salivary gland swelling in Sjögren syndrome and lymphomas is termed the 'benign lymphoepithelial lesion', a histological rather than a clinical condition. It has recently been suggested that the lymphoepithelial lesion represents a localized lymphomatous process. HIV disease also predisposes to lymphomas, mainly non-Hodgkin's lymphomas, which are Epstein-Barr virus-related.
- Secondary tumours.
- Unclassified tumours.
- Tumour-like lesions (benign lymphoepithelial lesion, sialosis, oncocytosis).

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37 Sjögren syndrome

Key points

- Sjögren syndrome (SS) is the association of dry mouth and dry eyes.
- SS is an autoimmune disorder.
- 90% of SS patients are female.
- Dry eyes and mouth alone are termed sicca syndrome or primary SS.
- Dry eyes and mouth with a connective tissue disease are termed secondary SS.
- Dry mouth predisposes to difficulties speaking and swallowing.
- Complications may include caries, candidiasis and sialadenitis – and lymphoma.
- Diagnosis is confirmed by detection of serum autoantibodies SS-A and SS-B, and other investigations. Diagnosis can be aided by a salivary gland biopsy.
- Management is with sialogogues and salivary substitutes and preventive dentistry.

Introduction

Sjögren syndrome (SS; Gougerot-Sjögren syndrome) is an autoimmune disorder in which immunocytes damage the salivary and lacrimal glands, and other exocrine glands. Dry mouth and dry eyes are seen with lymphoid infiltrates in these and other exocrine glands, and serum autoantibodies (Fig. 37.1).

SS has two main forms (Table 37.1):

- Primary Sjögren syndrome (SS-1), in which dry eyes and dry mouth are seen, in the absence of a connective tissue disease. This is uncommon and sometimes termed 'sicca syndrome', but the latter term is also used non-specifically for dry mouth and eyes.
- Secondary Sjögren syndrome (SS-2), which comprises dry eyes and dry mouth together with a connective tissue disease, is more common. The connective tissue association is usually with (in descending order of frequency):
 - rheumatoid arthritis (RA)
 - systemic lupus erythematosus
 - polymyositis
 - scleroderma.

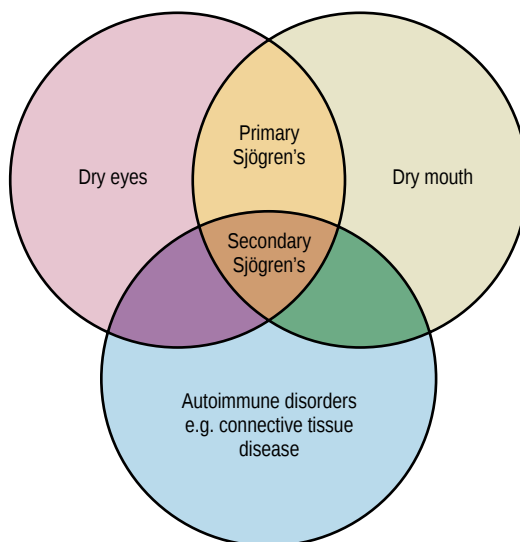


Fig. 37.1 Sjögren syndrome

Table 37.1
Sjögren syndrome: comparison of subtypes

Feature	SS-1	SS-2
Connective tissue disease	–	+
Oral involvement	More severe	Less common
Ocular involvement	More common	Less common
Recurrent sialadenitis	More common	Less common
Lymphoma	More common	Less common
Main serum autoantibody	SS-B	SS-A

Incidence

SS itself is uncommon, although the very rarity may lead to underdiagnosis.

Age

SS can affect any age, but the onset is most common in middle-age or older.

Sex

The majority of patients affected by SS are women.

Geographic

There is no known geographic incidence to SS.

Predisposing factors

See Figure 37.2.

- Sjögren syndrome may have a genetic basis: there is association especially to HLA class II antigens HLA-DRB1*15-DRB1*0301 and TAP1-0101 TAP2-0101. SS is sometimes found in other family members and it is also found more commonly in families that have members with other autoimmune disorders.
- A Sjögren-like syndrome can be produced by viruses [Epstein-Barr virus, hepatitis C virus, HIV, human T lymphotropic virus 1 (HTLV-1)].
- A Sjögren-like syndrome can be produced by graft-versus-host-disease (see Ch. 40).

Aetiology and pathogenesis

- The antigen in SS is unknown, but viruses may be implicated.
- The autoimmune response usually mainly affects exocrine glands, particularly the salivary, lacrimal, and vaginal.
- The lungs, brain, nerves, joints, kidneys, thyroid and liver can also be affected in SS.
- Autoantibodies found in SS are commonly against:
 - IgM (rheumatoid factor – an IgG antibody against IgM)
 - ribonucleoproteins, especially Sjögren syndrome-A (SS-A or Ro), and SS-B (La)
 - others antigens such as:

- alpha-fodrin
- alpha-amylase
- muscarinic M3 receptor
- carbonic anhydrase
- actin
- salivary duct. However, in sicca syndrome (where oral symptoms are typically more severe) these are less frequently found than in secondary SS, suggesting they may be causally unrelated to the duct damage.

Fragmentation of autoantigens such as La (SS-B) or alpha-fodrin during apoptosis (cell death) causes the redistribution of these autoantigens, leading to the production of the autoantibodies in SS (Fig. 37.3).

- SS appears to be the result of lymphocyte-mediated destruction of exocrine glandular acini, which starts with periductal infiltration initially mainly by B but later mainly by T lymphocytes (Fig. 37.4). The distribution of the membrane pore channel (water channel) protein aquaporin-5 is abnormal in SS, perhaps as a result of paracrine effect of TNF-alpha, and the neurogenic regulation of the salivary gland also becomes impaired (Fig. 37.5). One theory is that Sjögren syndrome is caused by a deficiency of suppressor T lymphocytes and subsequent overactivity of B lymphocytes, with release of interleukin-10 (IL-10) and the production of autoantibodies. Anti-muscarinic3 receptor antibody plays an important role in cholinergic hyper-responsiveness in SS. CD40/CD40L (CD40 ligand) and Bcl-2 family proteins, in tandem with B cell-activating factor (BAFF), protect infiltrating lymphocytes from apoptosis.
- Although the gland acini atrophy, the duct epithelium tends to persist and proliferates – sometimes to the extent that the duct lumens may become obliterated, producing islets of epithelium known as ‘epimyoepithelial islands’. The fully developed lesion of SS in major glands thus appears as a dense mass of lymphocytes interspersed by islands of epithelium, a pattern termed the ‘benign lymphoepithelial lesion’ (BLL). Occasionally, BLL exist in the absence of serological and other features of SS.
- B-cell overproduction may eventually lead to lymphoma (Fig. 37.6).

Clinical features

Sjögren syndrome has a clinical spectrum that extends from an organ-specific autoimmune process to a systemic disorder. The early manifestations may be non-specific, such as fatigue, arthralgia, and Raynaud’s phenomenon, and it can be 8–10 years from the initial symptoms to full-blown SS. Since the signs and symptoms can be so subtle

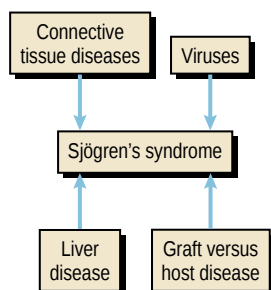


Fig. 37.2 Sjögren syndrome: possible aetiological factors

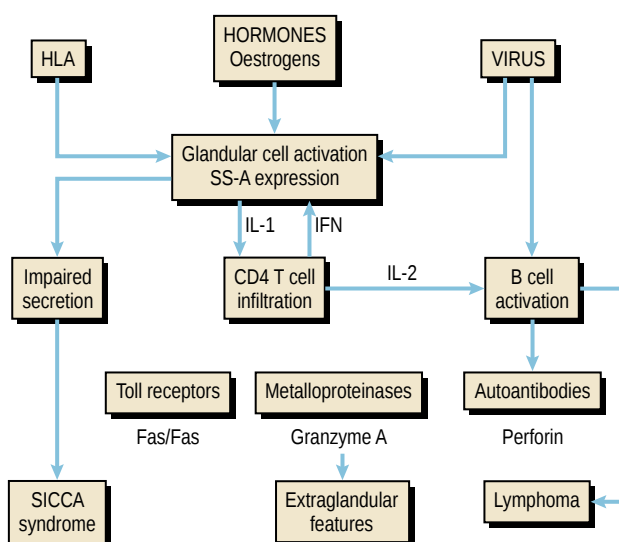


Fig. 37.3 Sjögren syndrome: pathogenesis

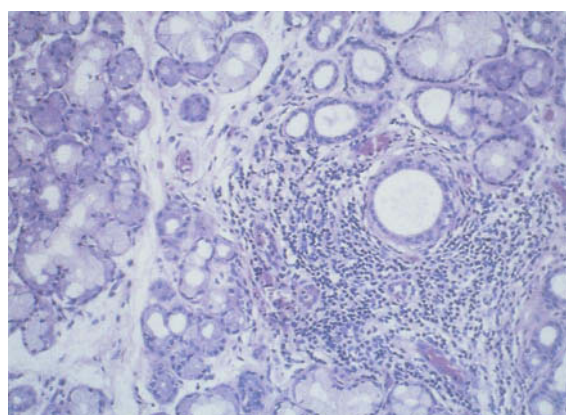


Fig. 37.4 Sjögren syndrome: histopathology showing dense lymphocytic periductal infiltrate (focal sialadenitis)

and non-specific, a thorough history and careful physical examination are mandatory.

SS presents mainly with (Box 37.1):

- eye complaints, including sensations of grittiness, soreness, itching, dryness, blurred vision or light intolerance. The eyes may be red with infection of the conjunctivae and soft crusts at the angles (keratoconjunctivitis sicca). The lacrimal glands may swell
- oral complaints (often the presenting feature), including:
 - xerostomia: often the most frequent and obvious clinical component, although not all patients complain of dry mouth (Fig. 37.7)
 - soreness or burning sensation
 - difficulty eating dry foods, such as biscuits (the cracker sign)
 - difficulties in controlling dentures

- difficulties in speech: there may be a clicking quality of the speech as the tongue tends to stick to the palate
- difficulties in swallowing
- complications such as unpleasant taste or loss of sense of taste; oral malodour; caries; candidiasis; sialadenitis.

Oral and salivary gland examinations are important. The mouth may appear dry, and on examination there may be:

- tendency of the mucosa to stick to a dental mirror
- food residues (Fig. 37.8)
- lack of salivary pooling
- frothiness of saliva and absence of frank salivation from major gland duct orifices
- a characteristic tongue appearance; lobulated, usually red, surface with partial or complete depapillation
- in advanced cases – obviously dry and glazed oral mucosae.

Oral complications

- Unpleasant taste, loss of sense of taste or malodour.
- Candidiasis is common and may cause soreness and redness of the oral mucosa or angular cheilitis.
- Dental caries tends to be severe, affect smooth surfaces and is difficult to control.
- Ascending (suppurative) sialadenitis is a hazard.
- Salivary gland enlargement is not uncommon in Sjögren syndrome. It is:
 - usually caused by the SS inflammatory process
 - intermittently caused by bacterial ascending infection (acute sialadenitis; Fig. 37.9)

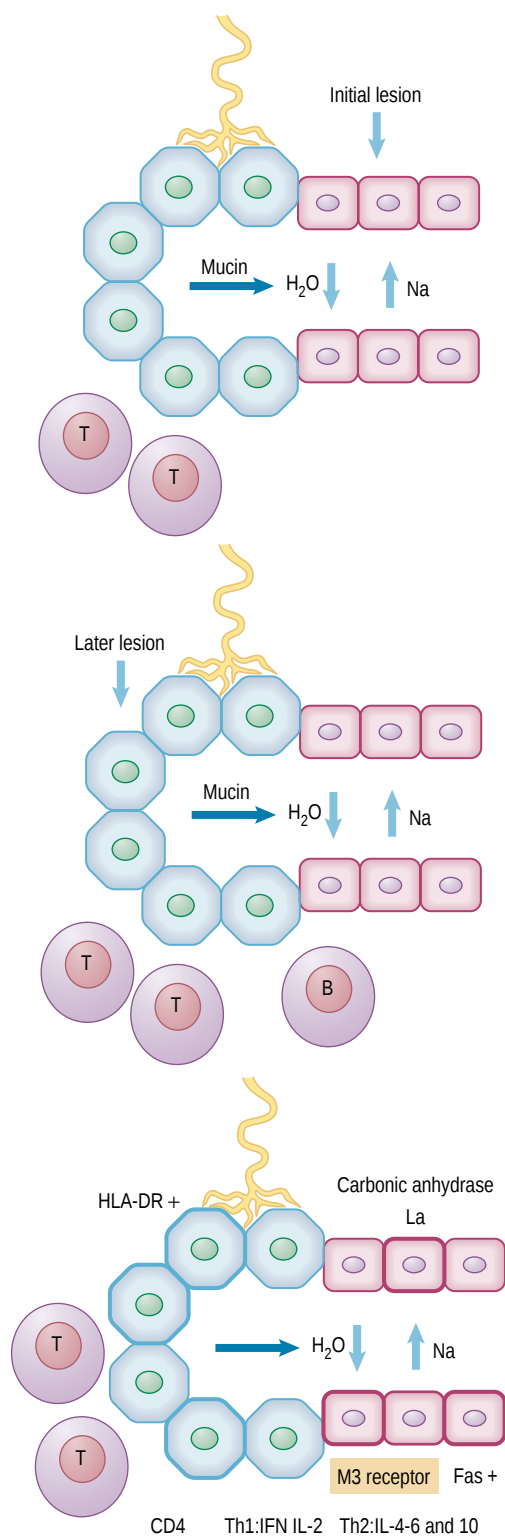


Fig. 37.5 Sjögren syndrome showing evolution of salivary lesion

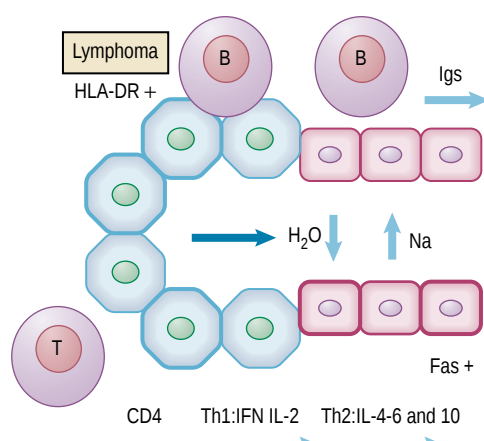


Fig. 37.6 Sjögren syndrome showing evolution to lymphoma

Box 37.1

Sjögren syndrome main features

Oral signs and symptoms

- Dry mouth
- Cracker sign
- Burning
- Salivary swelling and sialadenitis
- Caries
- Candidiasis
- Abnormal taste
- Malodour

Ocular signs and symptoms

- Foreign body sensation
- Inability to tear
- Light intolerance

Others

- Fatigue
- Fever
- Kidney, muscle, nerve, liver, joint, thyroid involvement
- Connective tissue disease

- occasionally massive and associated with enlargement of the regional lymph nodes, a condition called 'pseudolymphoma'
- rarely due to lymphoma.
- Mikulicz's disease (MD) is the term given to persistent salivary and lacrimal gland enlargement associated with raised serum immunoglobulin G4 (IgG4) and prominent infiltration of IgG4-expressing plasmacytes in the lacrimal and salivary glands. It is characterized by few autoimmune reactions and good responsiveness to corticosteroids; complications include autoimmune pancreatitis, retroperitoneal fibrosis, tubulointerstitial nephritis, autoimmune hypophysitis and Riedel's thyroiditis.



Fig. 37.7 Sjögren syndrome showing dry mouth



Fig. 37.9 Sjögren syndrome showing salivary swelling



Fig. 37.8 Sjögren syndrome showing food residues in vestibule

Extraoral complications

- Connective tissue disease in SS usually precedes the onset of dry eyes and dry mouth, and, therefore, patients presenting with dry eyes and dry mouth alone probably have primary SS, unless a connective tissue disease manifests within about 1 year. The connective tissue disease in secondary SS is typically longstanding and should be clinically obvious; rheumatoid arthritis is the most common.
- Extraglandular complaints of SS can include (Fig. 37.10):
 - Raynaud phenomenon
 - arthralgia
 - myalgia
 - fatigue
 - skin ulceration or rash
 - dyspnoea
 - dry vagina
 - bruising, bleeding and purpura
 - numbness and other neurological features.
- Associations of SS can include:
 - autoimmune (Hashimoto's) thyroiditis
 - gastro-oesophageal reflux disease (GORD)
 - primary biliary cirrhosis
 - malignant or pseudomalignant lymphoproliferation. Mostly in primary SS, these are B-cell lymphomas, which result from B-cell lymphoproliferation in mucosal-associated lymphoid tissue (MALT lymphoma) and which may develop into monoclonal gammopathies (such as Waldenström's macroglobulinaemia). Pseudolymphoma or frank lymphoma should be suspected when there is persistent salivary gland enlargement, lymphadenopathy or lung nodules. Mixed monoclonal cryoglobulins may be found, and when these contain rheumatoid factor cross-reactive for V kappa IIIb related or VH1-related idiotypes, they may be markers for lymphoma.

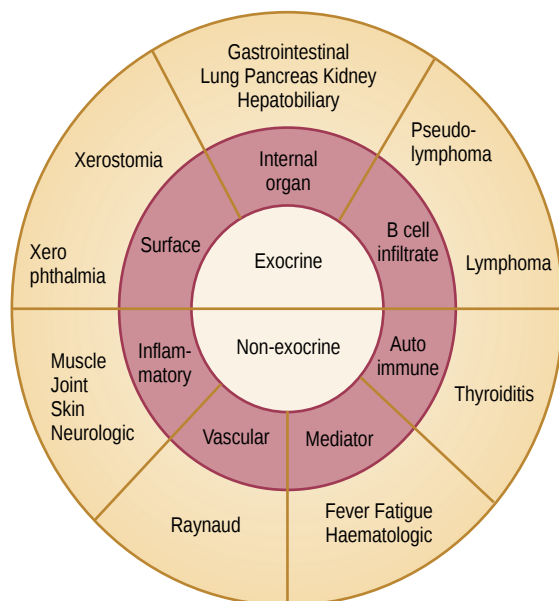


Fig. 37.10 Sjögren syndrome – extraglandular complications

- In pregnancy in SS, the autoantibodies may move transplacentally and cause fetus/infant heart block.

Diagnosis

A subjective feeling of dry mouth (xerostomia) is common, although reduced salivary flow (hyposalivation) is not always confirmed by objective studies (see Ch. 8). Indeed, of older people 16–25% complain of xerostomia – usually caused by drugs. If SS is suspected; however, specialist referral is warranted since investigations may be needed, and the differential diagnosis may include:

- viral infections:
 - hepatitis C virus
 - HIV
 - HTLV-1
 - EBV
- sarcoidosis
- glandular deposits in:
 - haemochromatosis
 - lipoproteinaemias
 - amyloidosis
- lymphomas.

The diagnosis of SS is mainly on the history, clinical examination and investigation, including:

- ocular symptoms
- oral symptoms

- ocular signs
- autoantibodies
- salivary gland involvement
- histopathology.

The American–European diagnostic criteria (revised) for Sjögren syndrome are shown in [Box 37.2](#).

Eye examination

Examination of the eyes by a specialist is most important ([Table 37.2](#)).

Autoantibodies and other blood tests

Autoantibody assays can be extremely helpful in diagnosis, and are readily available, inexpensive and fairly non-invasive. SS-A (Ro) and SS-B (La) antibodies are found especially in primary SS, may have diagnostic value in patients with unexplained parotid swelling and may antedate clinical evidence of Sjögren syndrome by months or years.

Blood tests may be indicated to:

- examine for SS-A and SS-B
- assess erythrocyte sedimentation rate (ESR) or plasma viscosity
- exclude anaemia
- examine IgA immune complexes
- exclude similar syndromes seen in infection with hepatitis C virus, EBV, HTLV-1 or HIV.

Salivary gland examination

Salivary gland examination, functional studies and biopsy may be indicated ([Box 37.2](#), [Table 37.2](#), [Algorithms 37.1](#) and [37.2](#)).

Salivary flow measurements (sialometry)

These are relatively simple and non-invasive, but are non-specific, and not especially sensitive. Objective evidence of diminished salivary flow in Sjögren syndrome includes a:

- decreased resting secretion rate of whole saliva <1.5ml in 15 minutes: this is more closely associated with symptoms of xerostomia than are stimulated flow rates. The test should be standardized by being carried out: after overnight fasting; first thing in morning; no food or drink for at least 1 hour before the test; no smoking for at least 1 hour before

► Box 37.2

Sjögren syndrome American–European diagnostic criteria*

SS is diagnosed if 4 of these 6 criteria are positive (especially if histopathology and serology are positive) or if there are ocular symptoms or oral symptoms, plus any 2 of the other 4 criteria:

Ocular symptoms

At least one of these:

- daily persistent troublesome dry eyes for >3 months
- recurrent sensation of sand or gravel
- need to use teardrops >3 times daily

Oral symptoms

At least one of these:

- daily feeling of dry mouth >3 months
- recurrent or persistently swollen salivary glands as adult
- frequently drink liquids to aid swallowing dry foods

Ocular signs

At least one of these:

- Schirmer <5mm in 5 minutes
- Rose–Bengal score >4

Histopathology

Focus score >1 on LSG†

Salivary gland involvement

At least one of these abnormal:

- scintigraphy – reduced concentration/uptake/excretion
- sialography – diffuse sialectasis
- unstimulated whole salivary flow <1.5ml in 15 min

Serum autoantibodies

At least one of these:

- SS-A (Ro)
- SS-B (La)

See Vitali et al (2002) for detail

*Focus = cluster of 50 or more lymphocytes in a labial salivary gland (LSG)

†Focus score = average number of foci in a 4 mm² area

Table 37.2
Salivary investigations in Sjögren syndrome

Investigation	Typical findings	Comments
Sialometry	Reduced	Non-specific, but readily available
Salivary gland biopsy	Focal lymphocytic infiltrate Acinar atrophy Fibrosis	More specific
Sialography	Sialectasis	Non-specific, but often available
Scintigraphy	Reduced radionuclide uptake	Non-specific, but expensive

Salivary gland biopsy

Biopsy of salivary glands can be useful in the diagnosis of Sjögren syndrome. Biopsy of major glands involves a skin incision and slight possibilities of facial nerve injury, scarring and salivary fistula. Therefore, minor salivary glands are usually biopsied.

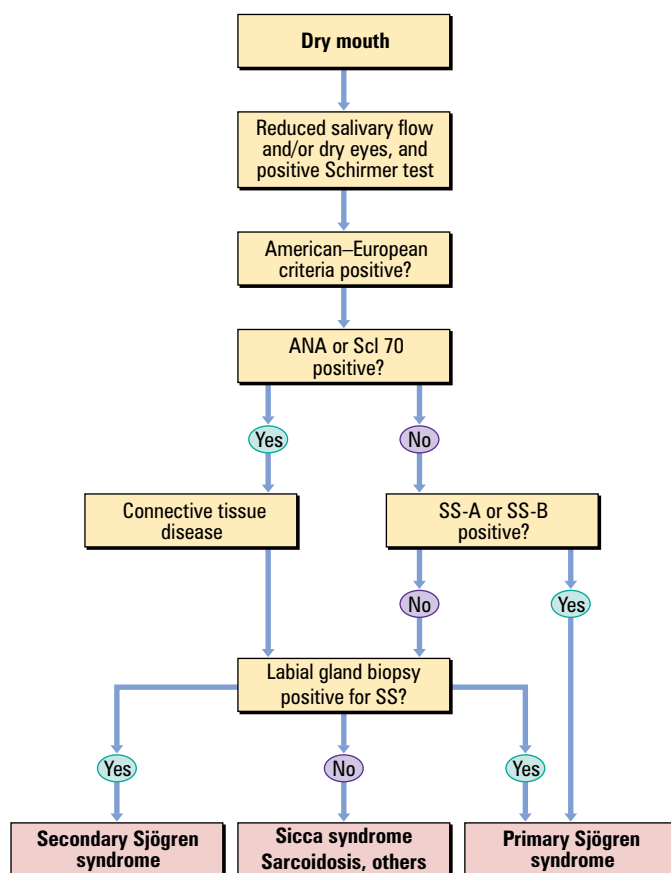
Minor glands in the palate and lower lip are accessible, but the latter site is preferred both from the aspects of patient comfort and access for the operator, and also because the extent and pattern of histopathological changes on labial salivary gland (LSG) biopsy correlate with those in parotid and submandibular glands.

The LSG biopsy technique involves: local analgesia; simple linear incision in the lower labial mucosa just to one side of the midline; at least five lobules of LSG are blunt dissected out and removed; and one or two sutures may be placed to ensure haemostasis. There are few adverse effects except occasional minor hypoaesthesia.

Focal sialadenitis is the characteristic histopathological feature. LSG histology, if used with a focus score (FS), provides a reproducible and objective evaluation of severity of inflammation. Other features such as fibrosis or fatty atrophy, duct dilatation and hyperplasia, however, are non-specific. A focus is defined as an aggregate containing 50 or more mononuclear cells: the FS is the number of such aggregates in each 4mm² area. The mononuclear cells are predominantly T-helper inducer cells. The FS is reliable only where gland lobes with acinar atrophy and interstitial fibrosis are excluded, and where an adequately large specimen is examined. The threshold FS generally used for diagnosis of SS is one focus per 4mm², though others use slightly higher thresholds. Focal sialadenitis in an adequate LSG biopsy (at least 4–5 lobules) appears to be the most disease-specific and sensitive diagnostic method.

the test; and with the patient being asked to dribble all their saliva into a measuring container for 15 minutes

- decreased stimulated flow rates: usually regarding flows of <0.5ml per gland in 5 minutes to 5ml per gland in 10 minutes as abnormal. Use various means of stimulation, such as 10% citric acid dropped on to the tongue, and collect parotid saliva using a Carlsson–Crittenden cup placed over Stensen's papilla.



Algorithm 37.1 Dry mouth diagnosis

Sialography

Sialography has the following characteristics:

- shows sialectasis (this is the most typical finding, it is most sensitive using oil-based contrast media and is seen particularly in parotid glands and may correlate with histological scores and scintigraphy)
- specificity is low
- time-consuming
- may be painful
- may produce hazards, such as granulomatous reactions or infection.

Salivary scintiscanning

Salivary scanning (scintigraphy) has the following characteristics:

- Shows diminished radionuclide uptake and spontaneous secretion, or secretion following citric acid or pilocarpine stimulation
- Is relatively non-invasive
- Examines both parotid and submandibular glands simultaneously

- Changes correlate with sialographic, flow rate and LSG histological changes, but are non-specific
- Quantitative registration of uptake and secretion phases with correction for vascular background might improve the diagnostic and monitoring value of salivary scintigraphy.

Ultrasonography

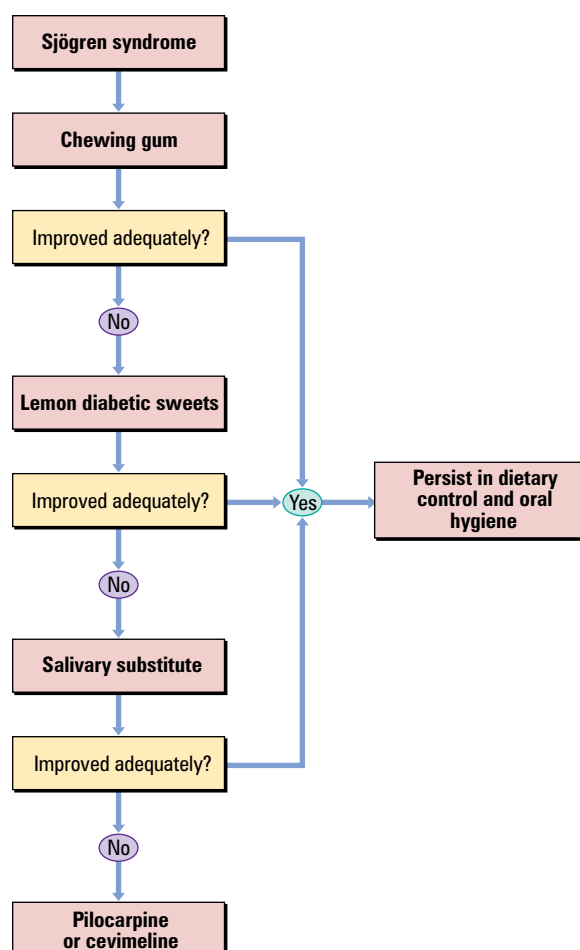
This is proving to be a useful method for evaluating salivary gland involvement in Sjögren syndrome and may replace other diagnostic techniques, such as sialography or salivary scintigraphy.

Magnetic resonance imaging

This can be helpful in showing soft tissue changes.

Sialochemistry

- Analysis of saliva composition (sialochemistry) for the diagnosis and monitoring of salivary disease has had some enthusiastic proponents, but has been of no



Algorithm 37.2 Sjögren syndrome management

practical value. It could prove to be of value in monitoring the disease process in view of the non-invasive nature. The diagnostically and prognostically most promising recent sialochemical findings have been of raised levels of:

- lactoferrin
- beta₂-microglobulin
- interleukin-6
- lysozyme
- sodium, chloride, albumin, lactoferrin, IgA and IgG (however, these are non-specific and rarely correlate with salivary flow or histological changes).

Management

- Sjögren syndrome remains an incurable condition, since no therapeutic modality has been identified that reliably modifies the course of the disease. Recently

there have been attempts to control the underlying autoimmune pathogenic mechanisms of lymphoid infiltration and cytokine release.

- Patient information is an important aspect in management.
- Any connective tissue or other disorders should be treated by a physician.
- Patients with severe extraglandular manifestations are usually treated by a physician with systemic corticosteroids and other immunosuppressive drugs.
- The patient should be followed up regularly, particularly because of the possible complication of lymphoma, which may manifest with:
 - firm tender persistent salivary swelling
 - lymphadenopathy
 - nodular lung lesions
 - cough
 - dyspnoea
 - hepatosplenomegaly.
- Other aspects of care include the following:
 - The use of a humidifier in the bedroom.

Patient information sheet**SJÖGREN SYNDROME**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon condition.
- The cause is unknown but it is immunological and possibly viral.
- It is not known to be infectious.
- It is not usually inherited.
- Dry mouth is common.
- Other mouth problems may include soreness, tooth decay and salivary swelling.
- Dry eyes are commonly found.
- Joint and other problems may be associated.
- Rarely, a very few patients may, after years, develop a tumour. You should get yourself checked regularly.
- X-rays, blood tests and biopsy may well be required.
- Symptoms can usually be controlled but not cured with simple drugs.
- Useful website: <http://www.sjsworld.org>.
- Advice is available from: British Sjögren's Syndrome Association, PO Box 10867, Birmingham, B16 0ZW (<http://www.bssa.uk.net>)

- For dry eyes, methylcellulose eye drops or, rarely, ligation or cauterization of the nasolacrimal duct.
- For dry mouth it can be helpful for the patient to: sip water or other fluids throughout the day; protect the lips with lip salve; take small bites of food; eat slowly; eat soft, creamy foods (casseroles, soups) or cool foods with a high liquid content (melon, ice cream); and to moisten foods with water, gravies, sauces, extra oil, dressings, sour cream, mayonnaise or yoghurt.
- It is wise for the patient to avoid: mouth-breathing; any drugs that may produce xerostomia (e.g. tricyclic antidepressants); alcohol (including in mouthwashes); smoking; caffeine (coffee, some soft drinks); dry foods, such as biscuits (or moisten in liquid first); spicy foods; and oral healthcare products containing sodium lauryl sulphate, which may irritate the mucosa.
- Salivation may be stimulated by using: chewing gums (containing xylitol or sorbitol, not sucrose); diabetic sweets; cholinergic drugs, such as pilocarpine or cevimeline that stimulate salivation (sialogogues) – which should be used by the specialist as discussed in Chapter 7; and translingual electrical stimulation.
- Salivary substitutes may help symptomatically. Various apart from water are available, including: methylcellulose; Saliva Orthana and Oralbalance are particularly useful since they contain fluoride (see Ch. 5) and mucin. However, there may be religious or cultural objections to use of mucin by some Muslims, Hindus, Jews and Rastafarians:

products containing carboxymethylcellulose (e.g. Glandosane or Luborant) may then be preferred.

- Complications should be avoided or managed by:
 - avoiding sugary foods
 - keeping the mouth clean
 - using fluorides
 - using mouthwashes of chlorhexidine.
- Dental caries is best controlled by dietary control of sucrose intake, and the daily use of fluorides as tooth-pastes, mouthwashes and gels (1% sodium fluoride gels or 0.4% stannous fluoride gels).
- Candidiasis may cause soreness or burning and, thus, should be treated with antifungals until there is neither erythema nor symptoms. Topical antifungals in liquid form, such as nystatin or amphotericin suspension, are the most effective and acceptable. Other preparations such as miconazole or fluconazole are also effective. Dentures should be left out of the mouth at night and stored in sodium hypochlorite solution, chlorhexidine or benzalkonium chloride to disinfect. An antifungal, such as miconazole gel or amphotericin, or nystatin ointment, should be spread on the denture before reinsertion
- Bacterial sialadenitis needs treating with a penicillinase-resistant antibiotic, such as flucloxacillin.
- Lymphomas; an oncological opinion is indicated; chemotherapy may be required.

Websites

Arthritis Link: <http://www.arthritislink.com/arthlinks.htm>

Sjögren's Syndrome Foundation: <http://www.sjogrens.org>

British Sjögren's Syndrome Association: <http://www.bssa.uk.net>

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Key points

- Temporomandibular joint (TMJ) pain–dysfunction syndrome refers to a common triad of jaw clicking, jaw locking (or limitation of opening) and/or pain.
- This afflicts young people mainly, typically teenagers or young adults.
- Trauma and stress appear to predispose.
- Diagnosis is essentially clinical.
- Management is variously by rest, exercise or other therapies.

Introduction

The temporomandibular joints (TMJ) are complex joints that need to work in concert, are essential to mastication, and are probably the most used joints in the body.

Temporomandibular joint pain–dysfunction syndrome [TMPD; myofascial pain dysfunction (MPD), facial arthromyalgia (FAM), mandibular dysfunction, or mandibular stress syndrome] refers to a common triad of joint symptoms:

- clicking
- jaw locking (or limitation of opening)
- pain.

This is one of the most common orofacial complaints and one of the controversial areas in dentistry in terms of aspects of aetiopathogenesis, diagnosis and management.

Incidence

The prevalence is at least 12% of the general population, but these symptoms have been reported at some time by up to 88% – with as many as 25% reporting severe symptoms.

Age

This disorder afflicts young adults mainly, typically teenagers and up to 20–30 years of age.

Sex

More patients are females than males.

Geographic

No known geographic incidence.

Predisposing factors

Trauma and stress appear to predispose.

Aetiology and pathogenesis

Hypotheses are many, but facts are few. TMJ dysfunction is a symptom complex of multifactorial aetiology, which almost certainly represents a psychological response to stress that becomes chronic through increasing muscle tension affecting the muscles of mastication (mainly the temporalis, masseter and pterygoid muscles).

Trauma

- Trauma including from road accidents, sports injuries, fights and dental extractions can be followed occasionally by TMJ dysfunction.
- TMJ dysfunction can be secondary to microtrauma and subsequent muscle hyperactivity, which can result from prolonged mouth opening, as in dental treatment sessions. Other causes of prolonged and/or excessive mandibular opening, e.g. general anaesthesia, choir singing or wind instrument playing, or parafunctions, such as day-time jaw clenching or night-time tooth grinding (bruxism), and habits, such as chewing a pen, can also lead to TMJ dysfunction.

Muscle hyperactivity

- Psychological stress can cause muscle hyperactivity. Depression and shortage of sleep are considered important risk indicators.

- Muscle hyperactivity has been demonstrated in TMJ patients during activities, such as school examinations and watching horror films.
- 50–70% of patients (twice as common as controls) have experienced stressful life events in the 6 months before onset. These problems concerning work, money, health, loss and interpersonal relationships probably have a causative role by inducing anxiety, which then produces increased jaw muscle activity.
- The two heads of the lateral pterygoid muscle have separate actions, the lower contracting during mouth opening, the superior head contracting during closing, to steady the meniscus as it moves back with the condyle into the glenoid fossa. During closing the lower head is electromyographically silent. In TMJ dysfunction patients, the lower head of the lateral pterygoid muscle contracts during the closing phase (when it should be relaxed). It has been suggested that anterior displacement of the TMJ meniscus, perhaps from a tear of the posterior capsule, prevents the superior head from acting effectively. The lower head perhaps attempts to help stabilize the meniscus. This might explain why this muscle is tender on palpation in TMJ dysfunction patients. Anterior displacement of the meniscus has been demonstrated by TMJ arthrography and found at operation in some TMJ dysfunction patients. Patients may be classified as having: no meniscus displacement; anterior displacement with reduction (excessive forward movement during opening which relocates on closing); and anterior displacement without reduction, when the meniscus remains anterior to the condyle in a buckled-up fashion, such that there is a reduced joint space and the articular surface of the condyle is close to the articular surface of the glenoid fossa. This latter situation predisposes to subsequent osteoarthritis.
- *Recurrent clicking in the TMJ*: clicking occurs either on attempted opening or closing. Often the click allows the completion of that phase of mandibular movement. Sometimes clicking ceases and the jaw locks either open or closed. Clicks are not diagnostic, since they are common in normal TM joints. A grating noise (crepitus) may signify intra-articular arthritic change, and there may be crepitus at any point of jaw movement, especially with lateral movements.
- *Limitation of jaw movement*: limitation of opening may be intermittent, with jaw 'locking'. There may be deviation of the jaw to the affected side on attempted opening with variable jaw deviation or locking, but rarely severe trismus. If there is reduced mouth opening this often suggests bilateral disease. Limitation may be more obvious on awakening, especially after nocturnal grinding. In some others, the limitation increases throughout the day.
- *Pain in the joint and surrounding muscles and elsewhere*: the main site is usually preauricular, but can radiate to the back of the mouth, down the neck, up to the temple or behind the ear. Pain may occur at an early stage or sometimes after the onset of clicking or stiffness of the jaw. It may range from a vague dull ache to an acute pain. Patients with a night-time clenching or grinding habit (bruxism) may awake with joint pain which abates during the day. The symptoms of individuals who clench or grind during working hours tend to worsen towards evening, and sometimes have a psychogenic basis. The pain may be aggravated by chewing or other jaw movements. There is often diffuse tenderness over masseters and temporalis muscles, which may be tender to palpation, but there is no detectable swelling. Sometimes pain is more clearly sited in a jaw muscle (e.g. the masseter or lateral pterygoid muscle), and sometimes trigger points can be located. Some patients may also complain of headaches, neck aches, and lower back pain. Female cases have significantly fewer children and are more likely to have never been pregnant, possibly due to fibromyalgia.

Possible dental causes

Abnormalities in the dental occlusion are controversial as causes of TMJ dysfunction. There is no neurophysiological evidence to support a primary aetiological role for the occlusion in TMJ dysfunction and many people with gross malocclusions have no TMJ dysfunction. There is no significant difference in the incidence of occlusal abnormalities between TMJ dysfunction patients and control subjects, nor is there any evidence for a relationship between orthodontic treatment (or the wearing of orthodontic headgear) and TMJ dysfunction.

Clinical features

Symptoms are highly variable, but dysfunction is characterized by:

Diagnosis

Diagnosis is mainly on clinical grounds. Self-ratings for psychological factors are helpful for assessment of the patient. The occlusion and any dental appliances should be assessed. Some clinicians use local anaesthetic injected in the joint to exclude TMJ arthritis as a cause. Symptoms can be quantified by the Helkimo indices based on both patient information (anamnesic dysfunction index, Ai) and clinical findings (clinical dysfunction index, Di) (Table 38.1). These indices include a numerical scoring system. Many patients presenting for treatment can be graded as AiII DiII/DiIII.

Table 38.1
Helkimo indices

Anamnestic index, Ai	Symptoms	Clinical dysfunction index, Di	Dysfunction
0	None	0	None
I	Mild: TMJ sounds; feelings of stiffness of the jaws	I	Mild
II	More severe: difficulty in opening the mouth wide; locking; fixation; pain on movement; facial and jaw pain	II	Moderate
		III	Severe

Imaging

Any osseous changes in organic joint disease, such as osteoarthritis or rheumatoid arthritis are unlikely, in the absence of longstanding disease, to be revealed by radiography. Indeed, radiographic changes are uncommon and the condylar position as seen on radiography is unreliable for diagnosis and does not indicate meniscus displacement. Arthrography, computed tomography (CT) or magnetic resonance imaging (MRI) are rarely indicated.

Imaging is not recommended for diagnosis, therefore, unless there is:

- a history of trauma
- significant limitation of movement, change in occlusion or a mandibular shift
- sensory or motor alteration
- a possibility of organic joint or other disease.

CT, MRI or OPT are then most useful but transpharyngeal, transcranial oblique lateral or transorbital condylar views can be helpful.

Other diagnostic procedures

There is no reliable scientific evidence to support the regular use of other suggested ‘aids’ such as:

- jaw tracking (mandibular kinesiology)
- electromyography
- electrovibratography
- sonography
- thermography.

Management

Patient information is an important aspect in management. TMJ dysfunction appears not to lead to long-term joint damage and some patients have spontaneous remission: thus, treatment is not always indicated. There is no indication, for example, for attempting treatment for TMJ clicks

Patient information sheet

TEMPOROMANDIBULAR PAIN–DYSFUNCTION

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is a common condition.
- It appears to be related to stress, damage or habits involving the teeth and joints.
- It is not inherited.
- There are no serious long-term consequences; arthritis does not result.
- The symptoms usually clear spontaneously after some months.
- Various treatments, such as rest, exercises, drugs, ointments, splints or adjustments to the teeth may help.
- Useful websites:
 - <http://www.aaop.org>
 - <http://www.tmjd.com>.

that are otherwise symptomless. However, in persons who complain of pain, treatment may be worthwhile. The level of placebo response and the response from reassurance is impressive, and conservative measures are at least partially successful in up to 90% – usually within 6 months. Of the other 10%, half may be functional and respond to psychotropic medication and the rest are chronic pain sufferers.

The aims of treatment are to:

- control immediate pain
- lower psychological stress (reassure)
- eliminate TMJ damage.

Possible treatments

There is a wide range of treatments offered for TMJ dysfunction, including physical, medical, psychological and surgical approaches:

- Physical treatments include:
 - occlusal adjustments
 - occlusal reconstruction

Patient information sheet**TEMPOROMANDIBULAR PAIN-DYSFUNCTION
FOUR STEPS TO MANAGE JAW PAIN**

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

Rest yourself and your jaw:

- relax and practice stress reduction
- exercise regularly
- eat soft foods and avoid hard, crusty foods like nuts or hard bread or those that need chewing a great deal
- chew on your back teeth, not the front ones
- eat small bites
- sleep on your side.

Avoid joint or muscle damage by avoiding:

- contact sports (wear a mouthguard if you must play contact sports)
- excessive jaw use in yawning, grinding and clenching
- chewing gum
- habits, such as biting finger nails, pens and pencils or lip
- long dental appointments or general anaesthesia
- cradling the telephone between head and shoulder
- wind instrument playing.

Reduce muscle pain with analgesics and by applying:

- cold packs for 10 minutes every 3 hours for 72 hours after injury
- hot packs for 20 minutes every 3 hours to uninjured joints/muscles.

Re-educate the jaw opening:

- open your mouth with a hinge movement
- exercise your jaw twice daily, opening 5 times in front of a mirror, ensuring the jaw opens vertically downwards without deviating sideways
- exercise your jaw three times daily for 5 timed minutes:
 - close your mouth on the back teeth
 - put the tip of your tongue on the palate behind your front teeth
 - move the tongue back across the palate as far as it will go
 - keep the tongue in this position with the teeth closed for 10 seconds
 - open your mouth slowly until the tongue starts to leave the palate
 - keep that position for 10 seconds
 - close your mouth
 - repeat over 5 minutes.

- occlusal soft covers (e.g. polythene vacuum-formed cover)
- immobilization
- muscle exercises
- mandibular orthopaedic repositioning appliance.
- Medical treatments include:
 - rest
 - heat
 - cold
 - transcutaneous electrical nerve stimulation

- analgesics (non-steroidal anti-inflammatory drugs)
- muscle relaxants (e.g. benzodiazepines)
- antidepressants (e.g. tricyclics)
- injections
- trigger-point (peri-articular) local analgesics
- intra-articular corticosteroids.
- Psychological treatments:
 - psychiatric treatment
 - group therapy
 - behaviour modification/biofeedback
 - hypnosis.
- Surgical treatments:
 - condylotomy (rarely, high condylar shave; high partial condylectomy indicated)
 - capsular rearrangement
 - silicone or Teflon implants
 - auriculotemporal nerve section.

Treatment regimens

A typical treatment regimen includes:

- rest
- avoidance of trauma, wide opening and abnormal habits
- warmth, massage and remedial jaw exercises to control discomfort
- analgesics; non-steroidal anti-inflammatory agents such as aspirin can be helpful. Ibuprofen-containing gel may help. Injection of local analgesics into painful sites, or the spraying of coolants, such as trichlorofluoromethane onto the areas, can ease pain and break the cycle
- muscle relaxants such as clonazepam 0.25mg/day, temazepam 10mg, or baclofen 10mg three times daily can help provide relief.

If these prove insufficient, it may be helpful to:

- use plastic splints on the occlusal surfaces (occlusal splints). It is unclear how these function, but they increase the vertical dimension, may reduce joint loading, eliminate faulty occlusal interferences, and probably most importantly provide cognitive awareness of damaging oral habits and engender a placebo effect. In any event, at least 40% benefit symptomatically, especially from hard splints.
- relieve obvious occlusal interferences and to correct prosthetic discrepancies, such as an incorrect vertical dimension; however, any possible benefits from major occlusal alterations must be set against a high placebo response and the important role of reassurance.
- use biobehavioural modalities (psychotherapy, biofeedback, relaxation), anxiolytic agents or antidepressants. These include:
 - diazepam 2mg three times daily
 - lorazepam 1mg/day
 - alprazolam 0.25mg three times daily
 - temazepam 10mg/day.

The remaining subgroup of 5–10% of patients may need treatment for prominent psychological problems by either medication or psychiatric therapy. The very small minority of patients who fail to respond to the above measures may require local corticosteroid (triamcinolone or depomedrone) or hyaluronate or a sclerosant therapy. Surgery may be required for the very small number of remaining non-responders, especially those with obvious intra-articular pathology (osteoarthritis).

Websites

TMJ Association: <http://www.tmj.org/home.asp>
<http://www.entnet.org/tmj.html>

Further reading

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39

Trigeminal and other neuralgias

Key points

- Trigeminal neuralgia (TN) consists of severe paroxysmal orofacial affects pain which last a few seconds.
- Pain is in one or more divisions of the trigeminal nerve.
- Pain is sometimes triggered by touching areas or by certain daily activities, such as eating, talking, washing the face, shaving or cleaning the teeth.
- There is no neurological deficit.
- Organic cause of neuralgia must be excluded by history, physical examination and special investigations.
- Treatment is primarily and essentially medical, with an anticonvulsant, such as carbamazepine.
- Surgery is reserved for recalcitrant TN.

Introduction

Sensory innervation of the mouth, face and scalp depends on the fifth cranial (trigeminal) nerve (Figs 39.1 and 39.2), so that disease affecting this nerve can cause orofacial pain or sensory loss, or, indeed, both, sometimes with serious implications. The term 'neuralgia' means pain in a nerve. Trigeminal neuralgia (TN) is a disorder of the trigeminal nerve that causes episodes of unilateral intense, stabbing, electric shock-like pain in the areas of the face where the branches of the nerve are distributed – lips, eyes, nose, scalp, forehead, upper jaw or lower jaw. TN is not fatal, but it is universally considered to be one of the most painful afflictions known.

Trigeminal neuralgia with no obvious neurological cause

This is also known as idiopathic trigeminal neuralgia, benign paroxysmal trigeminal neuralgia, trigeminal neuralgia and tic douloureux.

Incidence

Uncommon, probably about 4 cases per 100 000 population, although TN is the most common neurological cause of facial pain.

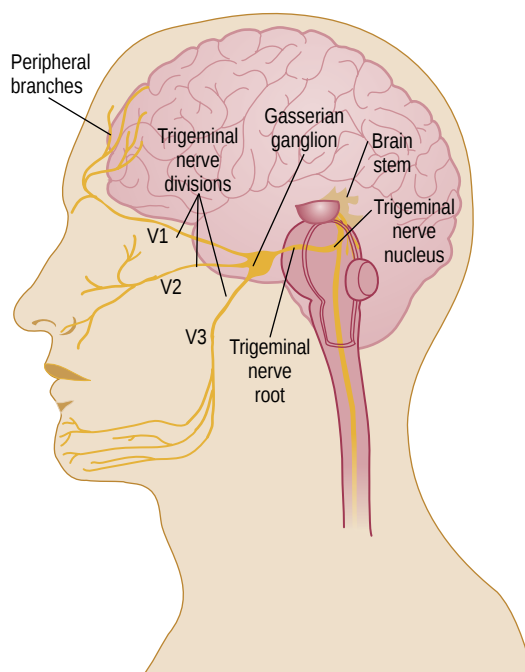


Fig. 39.1 Trigeminal nerve anatomy

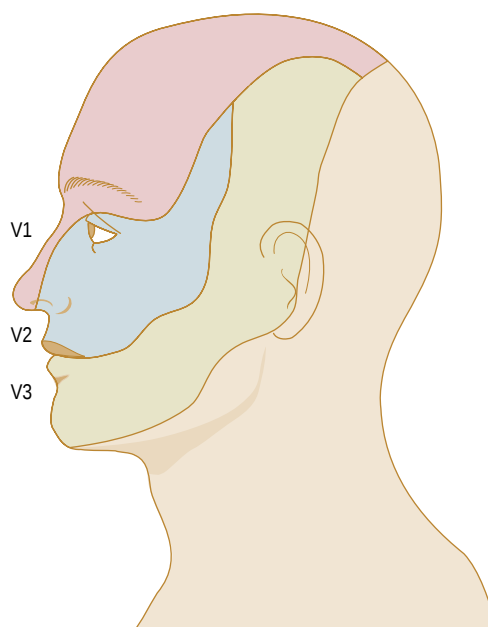


Fig. 39.2 Trigeminal nerve sensory distribution by divisions

Age

TN onset is mainly in the 50–70 year age group. Symptomatic or secondary TN tends to occur in younger patients.

Sex

TN is slightly more common in women.

Geographic

There is no known geographic incidence.

Predisposing factors

Severe orofacial pain suggestive of trigeminal neuralgia, but with physical signs, such as facial sensory or motor impairment, can result from cerebrovascular disease, multiple sclerosis, infections such as HIV infection, or space-occupying lesions, such as neoplasms or aneurysms, or lesions may irritate trigeminal nerve roots along the pons. No predisposing factors have been identified for *idiopathic* trigeminal neuralgia, but emotional or physical stress can increase the frequency and severity of attacks.

Aetiology and pathogenesis

The cause is unclear, but one hypothesis for idiopathic TN is that there may be compression around the trigeminal root in the posterior cranial fossa, possibly due to the superior cerebellar artery becoming atherosclerotic and, therefore, less flexible, and then pressing on the roots of the trigeminal nerve, causing neuronal discharge.

Clinical features

TN pain distribution is unilateral and follows the sensory distribution of cranial nerve V, typically radiating to the maxillary (V2) or mandibular (V3) area (Fig. 39.2). Idiopathic TN has the following main characteristics as defined by the International Headache Society:

- Paroxysmal attacks of facial pain that last a few seconds to less than 2 minutes; occurring especially in the morning, rarely at night.
- Pain has at least four of the following characteristics:
 - a distribution along one or more divisions of the trigeminal nerve
 - a sudden intense, sharp superficial, stabbing or burning quality
 - the pain intensity is severe

- precipitation from trigger areas or by certain daily activities, such as eating, talking, washing the face, shaving or cleaning the teeth
- the patient is usually entirely asymptomatic between paroxysms, but some patients experience a dull ache at other times.
- There is no neurological deficit.
- The attacks are stereotyped in the individual patient.
- Exclusion of other causes of facial pain by history, physical examination and special investigations when necessary.

A less common form of the disorder, called 'atypical trigeminal neuralgia', may cause less intense, constant, dull burning or aching pain, sometimes with occasional electric-shock-like stabs, usually unilaterally, but some patients experience pain on both sides. Patients with atypical trigeminal neuralgia may occasionally be developing mixed connective tissue disease (MCTD).

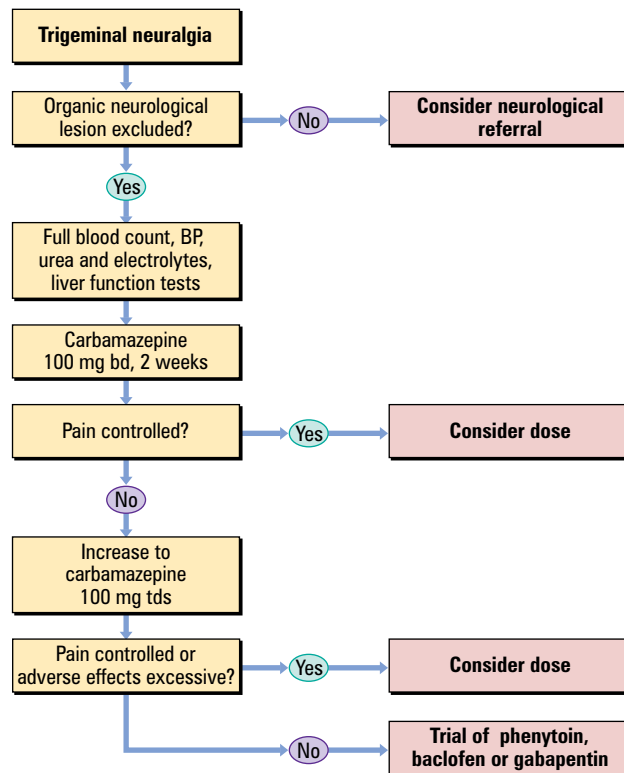
Diagnosis

Although TN typically is caused by a dysfunction in the peripheral nervous system (the roots or trigeminal nerve itself), a lesion within the central nervous system may rarely cause similar problems and must, therefore, be excluded (Algorithm 39.1) by:

- history
- examination, including neurological assessment, especially of the cranial nerves
- investigations, including:
 - imaging by radiography, magnetic resonance imaging (MRI) or computed tomography (CT) to exclude cerebral space-occupying or demyelinating lesions. Many physicians recommend elective MRI for all patients to exclude an uncommon mass lesion or aberrant vessel compressing the nerve roots or demyelination, but it is certainly mandatory if atypical features are present
 - blood tests, e.g. possibly erythrocyte sedimentation rate (ESR) to exclude vasculitides, anti-RNP antibodies for MCTD, and serology for Lyme disease or, rarely, HIV.

Management

- Patient information is an important aspect in management.
- TN is often an intermittent disease with apparent remissions for months or years, but recurrence is common and very often the pain spreads to involve a wider area over time and the intervals between episodes tend to shorten. Few patients have spontaneous remission and, thus, treatment is usually indicated.



Algorithm 39.1 Trigeminal neuralgia management

Patient information sheet

TRIGEMINAL NEURALGIA

Please read this information sheet. If you have any questions, particularly about the treatment or potential side-effects, please ask your doctor.

- This is an uncommon disorder.
- The cause is unknown, but involves spontaneous activity of pain nerves.
- It is not inherited.
- It is not known to be infectious.
- Similar symptoms may be seen in some neurological conditions (which we will exclude).
- There are usually no long-term consequences.
- X-rays, scans and blood tests may be required.
- Symptoms may be controlled, but not cured, by drugs with an anticonvulsant action.
- Uncontrolled pain may be treated by freezing the nerve, or surgery.
- Useful websites:
 - <http://www.painfoundation.org>
 - <http://www.tna-support.org>

Medical treatment

Medical treatment is used successfully for most patients, typically using anticonvulsants, especially carbamazepine, which is related to the tricyclic antidepressants. Hard evidence that the non-anticonvulsants can be effective is lacking.

Carbamazepine:

- is the main anticonvulsant used for control of trigeminal neuralgia
- prevents attacks of neuralgia in 60% of patients
- must be given continuously prophylactically for long periods. It is not an analgesic and, if given when an attack starts, will not relieve the pain
- must be used carefully and under strict medical surveillance
- is contraindicated in pregnancy as it is teratogenic
- is typically given in 100mg doses twice daily for 2 weeks initially, then three times daily, increasing by 100mg every 3 days to a maximum of 1000mg/day. Most patients respond to 200–400mg carbamazepine three times daily
- dosage control can be effected by blood monitoring
- dose should be increased to control the pain, while at the same time avoiding ataxia and other adverse effects

- Patients with TN are best seen at an early stage by a specialist in order to confirm the diagnosis and initiate treatment.

- may cause adverse effects in up to one-third of patients, which include mainly:
 - ataxia
 - drowsiness
 - visual disturbance
 - headache
 - gastrointestinal effects
 - facial dyskinesias
 - folate deficiency
 - hypertension
- can cause other less common, but potentially serious, adverse effects, which include:
 - rashes, sometimes severe and exfoliative, though rarely life-threatening
 - pancytopenia or rarely leukopenia, which is idiosyncratic and typically occurs within the first 3 months of treatment
- requires monitoring of patients, which should include:
 - balance (disturbed – ataxia); this tends to be the feature that limits the dose of carbamazepine
 - blood pressure (may increase); patients must have a baseline test and then blood pressure estimations for 3 months, then 6-monthly
 - blood tests – electrolytes (sodium levels may be reduced – hyponatraemia); patients must have a baseline test and then monthly tests of urea and electrolytes; liver function [may be impaired; patients must have a baseline test and then liver function tests (bilirubin, transaminases) for 3 months, then 6-monthly]; bone marrow function (red and white cells and/or platelets may be depressed; patients must have a baseline and then monthly tests of red and white cell and platelet numbers, and corrected whole blood folate levels)
- may interact with cimetidine and isoniazid, potentiates lithium and interferes with oral contraceptives.

Some use a trial of baclofen since it has fewer adverse effects; the synergistic combination of carbamazepine and baclofen may provide relief. If this fails to control trigeminal neuralgia, phenytoin or other choices which may be effective include:

- antidepressants
- clonazepam
- gabapentin
- lamotrigine
- oxcarbazepine
- pregabalin
- sumatriptan
- topiramate
- valproate.

Some patients report having reduced or relieved pain by means of alternative medical therapies, such as acupuncture, chiropractic adjustment, self-hypnosis or meditation.

Surgical treatment

Should medication be ineffective, or if it produces excessive undesirable side-effects, four main surgical options are available:

- *Peripheral surgery*: which involves deliberately interrupting nerve conduction in a division or branch of the trigeminal nerve, and may bring temporary relief of analgesia without permanent anaesthesia. These procedures include:
 - local cryosurgery
 - injections of streptomycin or glycerol around the mandibular or infraorbital foramen
 - peripheral neurectomy of a whole division of the trigeminal nerve, using alcohol or phenol
 - radiofrequency thermocoagulation.
- *Open surgical procedures* include microvascular decompression of the trigeminal root (MVD) and retrogasserian rhizotomy – posterior cranial fossa procedures, which are successful in providing instant and prolonged pain relief, but with possible morbidity and even mortality. MVD is currently considered the gold-standard method – a major operation that repositions the artery that supposedly irritates the trigeminal nerve as it emerges from the brain stem.
- *Percutaneous approaches to trigeminal gangliolysis* by heating, compressing, or chemicals are considered to have less associated risk and less cost than do open surgical procedures. They can be done by inserting a needle into the skull through the face. Radiofrequency lesioning [RFL: percutaneous radiofrequency trigeminal gangliolysis (PRTG)] is the most commonly performed of these procedures. Percutaneous Fogarty balloon micro-compression (PBM), and percutaneous retrogasserian glycerol rhizotomy (PRGR) are also used. Pain is exchanged for anaesthesia (and, therefore, a risk of damage to the cornea) and, sometimes, continuous anaesthesia, but with pain (anaesthesia dolorosa).
- *Stereotactic Gamma Knife radiosurgery*, the newest treatment, is the least invasive and with the fewest adverse effects. It offers a high rate of pain control of approximately 80% without invasive surgery and with a low risk of facial paraesthesia, and a low pain recurrence rate. Its potential disadvantages include the use of radiation and the fact that benefit often takes 6 weeks or more to be considered successful.

Raeder paratrigeminal neuralgia

Severe persistent pain in and around the eye with an associated Horner syndrome (see Ch. 40) is often caused by a lesion at the base of the skull and requires neurological attention.

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia is much less common than trigeminal neuralgia. The pain is of a similar nature, but affects the throat and ear, and is typically triggered by swallowing or coughing. Carbamazepine is usually less effective than for trigeminal neuralgia and adequate relief of pain can be difficult, though gabapentin may be effective.

Occasionally, glossopharyngeal neuralgia is secondary to lesions (often tumours) in the posterior cranial fossa or jugular foramen (jugular foramen syndrome) and there are then often lesions of the vagus (X) and accessory (XI) nerves.

Herpetic and postherpetic neuralgia

Herpes zoster (shingles) is often preceded and accompanied by neuralgia. Neuralgia may also persist after the rash has resolved. Postherpetic neuralgia is pain in the trigeminal region that may follow an attack of zoster. It is seen mainly in the elderly. In half the patients the pain resolves within 2 months but in others it may continue for up to 2 years or longer.

Postherpetic neuralgia is defined by the International Headache Society as pain developing during the acute phase of herpes zoster and persisting more than 6 months thereafter.

Postherpetic neuralgia causes continuous burning pain that may be so intolerable that suicide can become a risk. Analgesics rarely relieve postherpetic neuralgia, and treatment is difficult, but there may be relief using:

- antidepressants (amitriptyline, desipramine or maprotiline)
- gabapentin
- oxycodone
- carbamazepine (see above)
- topical capsaicin 0.025% or lidocaine
- transcutaneous electrical nerve stimulation (TENS).

Spontaneous improvement may follow, however, after about 18–36 months in some patients.

Websites

Trigeminal Neuralgia Association: <http://www.tna-support.org>

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SECTION 4

RELEVANT AND OTHER SYSTEMIC DISORDERS

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- 42** Oral manifestations of disorders of specific systems 325

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40

Human immunodeficiency virus infection

Key points

- HIV is a lethal retrovirus infection transmitted by blood and body fluids.
- HIV damages lymphocytes leading to severe T cell immune defects.
- Defences against fungi, viruses, mycobacteria and parasites are especially impaired.
- Clinical disease (HIV disease) manifests after a long latency – with tumours, infections and other features.
- Common manifestations are Kaposi's sarcoma and lymphomas; infections with herpesviruses and papillomaviruses, candidiasis and cryptococcosis, tuberculosis, and toxoplasmosis.
- Acquired immune deficiency syndrome (AIDS) is the term used when the CD4 T lymphocyte count falls below 200 cells/ml.
- Antiretroviral therapy can prolong life in HIV/AIDS but can cause cardiac disease and many other adverse effects.

Human immunodeficiency virus disease

In healthy persons aged 5 years and older, with normally functioning immune systems, the CD4⁺ T-cell counts usually range from 500 to 1500 cells/ml. These immunocytes are crucial to host defences against fungi, viruses, mycobacteria and parasites.

Infection with the RNA retroviruses known as human immunodeficiency viruses (HIV) – formerly termed 'human T lymphotropic virus III' (HTL-III) – produces HIV infection which eventually damages T lymphocytes, especially those that are CD4⁺, thus causing immunodeficiency. This predisposes to infection with fungi, viruses, mycobacteria and/or parasites, and the appearance of clinical diseases, at which time the condition is termed 'HIV disease'. This then progresses over time to the acquired immune deficiency syndrome (AIDS), defined as a CD4⁺ T-lymphocyte count at or below 200 cells/ml in the presence of HIV infection. Premature death follows (Figs 40.1 and 40.2) though current anti-retroviral treatment can prolong life.

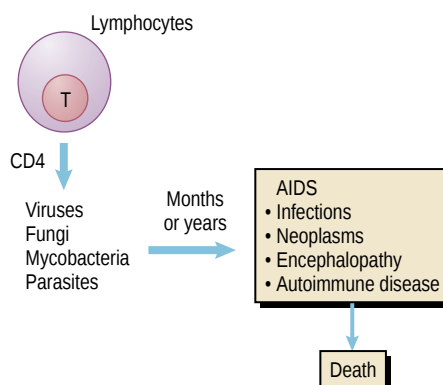


Fig. 40.1 Development of HIV/AIDS

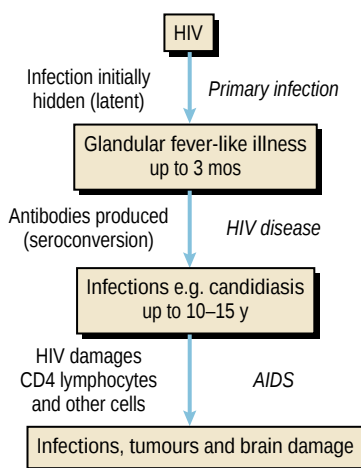


Fig. 40.2 Disorders in HIV/AIDS

Incidence

AIDS was first recognized in the USA in the early 1980s in the male gay populations, although the infection has subsequently been recognized to have existed in Africa some decades before then, at least in the 1950s. The epidemic has spread worldwide from an African epicentre, largely in the socially excluded and in the developing world where HIV/AIDS is a leading cause of death in young adults and is increasing in children. The incidence worldwide varies widely to a high of around 50% in some populations in sub-Saharan Africa.

Age

Worldwide, sexually active adults continue to be the age group mainly affected, but the number of cases in children continues to rise, largely through the increasing prevalence of infection in pregnant females.

Sex

Worldwide there is little if any difference in gender affected by HIV.

Geographic

The HIV epidemic:

- appears to have originated in sub-Saharan Africa, probably Zaire and Cameroon
- rate of increase has slowed in most parts of the developed world
- worldwide has spread mainly via heterosexual sex, although the incidence is still high in men who have sex with men (MSM)
- in the CIS and Asia is of major concern
- is not infrequently accompanied by infection with other blood-borne agents (e.g. hepatitis viruses) and/or sexually transmitted infections (e.g. syphilis).

Predisposing factors and transmission

HIV is present in tissues and body fluids (including blood and saliva) of HIV-infected persons. HIV is transmitted:

- readily through sharing needles and/or syringes (primarily for drug injection)
- commonly by unprotected sexual intercourse with an infected person. The risk of transmission via various sexual practices varies; anal intercourse is more risky than vaginal; and genital intercourse is more risky than orogenital or oroanal sex
- sometimes to babies born to HIV-infected women, before or during birth or through breast-feeding after birth
- less commonly (and now very rarely in countries where blood is screened for HIV), through transfusions of infected blood or blood clotting factors, or transplants
- rarely in the healthcare setting, by being stuck with needles or other sharps containing HIV-infected blood (needlestick injuries) or, less frequently, after infected blood has entered a worker's open cut or a mucous membrane (e.g. the mouth, eyes or inside of the nose)
- rarely by saliva, presumably because of protection from:
 - SLIP1 (secretory leukocyte protease 1)

- Peroxidases

- Thrombospondin-1

- transmission by recipient oral sex is far lower (estimated at 0.04%/per act) than is transmission by recipient anal sex (0.82%/per act).

Barrier precautions are highly effective at preventing transmission in all social and work situations, except for needlestick injuries. Transmission is best prevented by:

- **A** bstinence
- **B** faithful
- **C** ondom always.

Aetiology and pathogenesis

- There are two main HIV viruses responsible for HIV infection, but little difference between them in terms of pathogenesis, manifestations of infection, treatment or prognosis. There are also several strains of each virus:
 - HIV-1 is by far the most common worldwide
 - HIV-2 has spread from West Africa mainly.
- Infection with HIV infects cells with CD4 receptors.
- Infected CD4⁺ T-helper lymphocytes and brain glial cells become dysfunctional and die. The CD4 cell count falls (and there is a falling ratio of CD4/CD8 cells) and there is progressive immune deficiency and dementia.
- T-cell-mediated immune protection thus diminishes, and patients become predisposed to infection with yeasts and fungi, viruses, mycobacteria and parasites:
- Infections result from exogenous pathogens or from commensal organisms (i.e. they cause no or little obvious harm in the immunocompetent host); that become opportunistic pathogens:
 - Exogenous pathogens include especially *Pneumocystis carinii*, tuberculosis and atypical mycobacteria, such as *Mycobacterium avium-intercellulare*, the parasite *Toxoplasma gondii* and some mycoses.
 - Opportunistic pathogens include *Candida* species and other fungi, and some herpesviruses – especially herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human herpesvirus-8 (HHV-8). Some viruses may cause neoplasms; HHV-8 causes Kaposi sarcoma, EBV causes lymphomas and some human papilloma viruses (HPV) may cause cervical, anal and oropharyngeal carcinoma.

Clinical features

Acute HIV infection

Acute HIV infection passes unrecognized in the majority since features are non-specific. In one-third to one-half of those infected, during the 4–7-week period of



Fig. 40.3 Candidiasis in AIDS

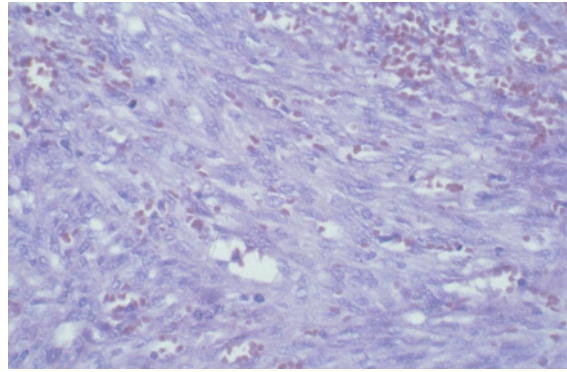


Fig. 40.5 Kaposi sarcoma histopathology



Fig. 40.4 Kaposi sarcoma

rapid viral replication immediately following exposure, there can be fever, malaise, lymphadenopathy, myalgia and other features closely mimicking glandular fever. Seroconversion and a broad HIV-1 specific immune response occur, usually within 30–50 days. High levels of HIV RNA are present in the blood.

HIV infection

This is an asymptomatic and variable period, often of years, when the virus is latent. There is a massive viraemia with wide dissemination of HIV to lymphoid organs, but the resulting immune response only partially suppresses HIV, and some virus escapes, leading to the gradual deterioration of immune function and CD4⁺ T cells.

HIV disease

HIV disease (symptomatic HIV infection) appears as the CD4 count progressively declines over a long incubation period, which may extend over 5–15 years or more. Then the person may develop:

- infections: the most important infections are *Pneumocystis carinii* pneumonia (PCP), candidiasis (Fig. 40.3), cryptococcosis, herpesviruses (especially HSV, VZV,

EBV and CMV) and parasites, such as toxoplasmosis and Leishmaniasis. Tuberculosis is increasing in HIV-infected persons in whom it may involve mycobacteria resistant to a range of antitubercular drugs (multi-drug-resistant tuberculosis: MDRTB or XRTB).

- neoplasms: the main tumours appear to be virally related and include Kaposi sarcoma associated with HHV-8 (Figs 40.4 and 40.5), lymphomas associated with EBV, and cervical or anal carcinomas associated with HPV.
- anorexia, diarrhoea, wasting, premature ageing and autoimmune phenomena, such as thrombocytopenia
- sometimes, neuropsychiatric disease: there may be dementia and other cerebral syndromes. A degenerative neurological condition characterized by a group of clinical presentations including loss of coordination, mood swings, loss of inhibitions and widespread cognitive dysfunction, is the most common central nervous system complication of HIV infection.

AIDS

AIDS is the most severe manifestation of HIV infection. The US Centers for Disease Control and Prevention list numerous opportunistic infections and neoplasms that, in the presence of HIV infection, constitute an AIDS diagnosis (Table 40.1) and, in 1993, the criteria for an AIDS diagnosis was expanded to include a CD4⁺ T-cell count at or below 200 cells/ml in the presence of HIV infection. Persons living with AIDS often have weight loss, diarrhoea, oropharyngeal candidiasis, infections of the lungs, brain, eyes and other organs, Kaposi sarcoma and lymphoma, and AIDS dementia complex.

Prognosis

The prognosis of HIV/AIDS has almost invariably been poor and death virtually inevitable, although there are rare patients who show remarkable genetic resistance. Antiretroviral agents have been developed that can significantly slow the progression of HIV disease.

Table 40.1
CDC classification of HIV and AIDS

CD4 count (cells/ml)	A Acute HIV infection, asymptomatic or PGL	B Symptoms and signs of progressive HIV infection, not AIDS	C AIDS
1 >500	A1	B1	C1
2 200–499	A2	B2	C2
3 <200	A3	B3	C3
Clinical features Fatigue Fever Malaise Weight loss Diarrhoea Lymphadenopathy Wasting Oral candidiasis Oral hairy leukoplakia Herpes zoster Immune thrombocytopenia Perianal herpes Splenomegaly Secondary neoplasms Kaposi sarcoma Lymphoma: primary of brain Non-Hodgkin's lymphoma		Opportunistic infections Disseminated cytomegalovirus Chronic disseminated herpes simplex Progressive multifocal leukoencephalopathy Tuberculosis Atypical mycobacterioses <i>Pneumocystis carinii</i> pneumonia Candidiasis of oesophagus, bronchi or lung Chronic cryptosporidiosis Toxoplasmosis of brain Isosporiasis Disseminated histoplasmosis Disseminated coccidioidomycosis Cryptococcosis Strongyloidiasis extraintestinally	

Oral features

Oral features of HIV/AIDS reflect the T-cell immune defect and are, thus, mainly the consequence of fungal or viral infections (Tables 40.1, 40.2 and Box 40.1):

- The most common are candidiasis (candidosis) and hairy leukoplakia.
- Necrotizing gingivitis, accelerated periodontitis, Kaposi sarcoma, lymphomas, salivary gland disease, ulcers of various infective aetiologies and other lesions may also be seen.
- Oral lesions may:
 - indicate HIV infection that is previously undiagnosed
 - be used in staging and therapy decisions
 - cause the patient pain or aesthetic problems
- These oral diseases have a number of common features, namely that generally they are:
 - not absolutely specific for HIV/AIDS, but are more a manifestation of the immune defect; thus similar lesions can be seen in other immune defects
 - generally more likely to manifest as the CD4 cell count falls to low levels
 - more likely to be seen where the oral hygiene is poor
 - more likely where there is also malnutrition
 - more likely if the patient smokes tobacco
 - often controlled, at least temporarily, by antiretroviral treatment (however, some lesions – such as

zoster and warts – have increased since the advent of ART; see below).

Diagnosis of HIV infection

Considerable compassion is required in the diagnosis of such a catastrophic infection, since it impacts on virtually all aspects of the person's life as well as that of their family and others, eventually resulting in unpleasant, painful and incapacitating illnesses and their treatment. Confidentiality must be maintained at all times and the patient's consent and views always sought, including when considering informing other healthcare workers of any details about the person involved. There must always be appropriate counselling:

- HIV infection at the very early stage may manifest no detectable antibody production and, thus, the test for serum HIV antibodies (serotesting) is negative – but this is then a false-negative result. At this stage only sophisticated tests for HIV RNA will detect the virus.
- HIV serum antibodies usually become detectable by 6 weeks.
- The enzyme-linked immunosorbent assay (ELISA) for HIV p24 antibodies is the main serological test used, but

Table 40.2
Oral lesions in HIV/AIDS

Type of disorder		Examples	Manifestations
Infection	Viral	Herpes simplex	Ulceration
		Herpes varicella zoster	Ulceration and pain
		Cytomegalovirus	Ulceration
		Epstein-Barr virus	Ulceration, lymphoma, hairy leukoplakia
		Human herpesvirus-8	Kaposi sarcoma
		Human papillomaviruses	Papillomas or warts
		Molluscum contagiosum	Papules
	Fungal	<i>Candida</i> <i>Cryptococcus neoformans</i> <i>Geotrichium candidum</i> <i>Histoplasma capsulatum</i> <i>Mucoracea</i> <i>Aspergillus</i>	White or red lesions, ulceration or lump
	Bacterial	<i>Mycobacterium tuberculosis</i> Non-tuberculous mycobacteria <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> <i>Actinomyces israelii</i>	Ulceration or lump
		<i>Bartonella (Rochalimaea) henselae</i> and <i>quintana</i>	Epithelioid angiomatosis
		Periodontal flora	See text
	Protozoal	Leishmania	Ulceration or lump
Autoimmune	Aphthous-like ulcers HIV salivary gland disease Thrombocytopenia		
Other	Facial palsy Trigeminal neuralgia Taste disturbance Exfoliative cheilitis Hyperpigmentation		

must be repeated and may need to be confirmed by a Western blot test. False test reactions are known, but rare.

Management of HIV disease

Few, if any, patients have spontaneous remission and, thus, treatment is almost invariably indicated, although in rare cases the disease progresses very slowly and may only at a very late stage manifest with serious complications. Patient information is an important aspect in management.

Since AIDS was first recognized about 20 years ago, remarkable progress has been made in improving the quality and duration of life of HIV-infected persons. This improvement has occurred because of:

- better recognition of opportunistic disease processes.
- better therapy for acute and chronic complications.
- the introduction of chemoprophylaxis against PCP, toxoplasmosis, *Mycobacterium avium* complex disease, and bacterial infections. Trimethoprim-sulfamethoxazole in particular reduces not only the incidence of PCP, but also of toxoplasmosis and bacterial infections.
- the development of antiretroviral therapy (ART). However, many drugs are liable to fairly severe adverse reactions and, perhaps more significantly, resistance has arisen (see Ch. 5). Combination antiretroviral therapy (CART) has increased life expectancy but also cardiac complications.

► Box 40.1

Classification of oral lesions in HIV disease

Group I: Lesions strongly associated with HIV infection

- Candidiasis:
 - erythematous
 - hyperplastic
 - thrush.
- Hairy leukoplakia (EBV)
- HIV gingivitis
- Necrotizing ulcerative gingivitis
- HIV periodontitis
- Kaposi sarcoma
- Non-Hodgkin's lymphoma

Group II: Lesions less commonly associated with HIV infection

- Atypical ulceration (oropharyngeal)
- Idiopathic thrombocytopenic purpura
- Salivary gland diseases:
 - dry mouth
 - unilateral or bilateral swelling of major salivary glands.
- Viral infections (other than EBV):
 - cytomegalovirus
 - herpes simplex virus
 - human papilloma virus (wart-like lesions) – condyloma acuminatum, focal epithelial hyperplasia and verruca vulgaris
 - varicella-zoster virus – herpes zoster and varicella

Group III: Lesions possibly associated with HIV infection

- A miscellany of rare diseases

- Protease inhibitors are used together with reverse transcriptase inhibitors as highly active antiretroviral therapy (HAART) (see Ch. 5).
- HAART has significantly reduced the incidence of most infections and extended life substantially. However, some infections, such as herpes zoster and HPV-induced warts have increased.
- In the era of CART, drug effects may cause more morbidity than AIDS.

There is some controversy as to the increase in cardiac disease and myocardial infarction, and at which point therapy should be introduced and as to the importance of prophylaxis of infections. Vaccines against HIV are still very much in their infancy.

Oral lesions in HIV disease

HIV-related oral candidiasis

Oral levels of *C. albicans* and other yeasts are increased in HIV infection, and infection is common.

Oral candidiasis is:

- the most common opportunistic infection in HIV-infected persons
- often the initial manifestation of symptomatic HIV infection
- seen at some point in at least 90% of HIV-infected patients
- seen in all groups at risk, especially HIV-infected intravenous drug users.

Oral candidiasis is related to:

- the immune defect; in general, the frequency of isolation of *Candida* species increases with increasing severity of HIV disease and with lower CD4 and/or CD4/CD8 ratios
- xerostomia and other salivary changes in HIV infection, such as reduced calprotectin, IgA, lactoferrin and anti-*Candida* antibodies
- smoking
- antimicrobial use.

Aetiology and pathogenesis

- Yeasts colonize the mouths of about 85% of HIV-infected persons.
- CD4 lymphocytes are deficient in the cellular infiltrate of candidal lesions in HIV infection.
- *Candida albicans* causes more than 85% of oral candidiasis, but up to 35 strains have been found.
- The strain of *Candida* usually remains constant. Recurrence is usually caused by a persistent strain, but occasionally a different strain appears and there may be sexual reinfection.
- *C. albicans* isolates from HIV-infected persons may show increased:
 - hyphal formation with epithelial invasion
 - aspartyl proteinase secretion
 - adherence to oral epithelial cells
 - resistance to antifungal drugs, especially amphotericin, itraconazole and fluconazole, even despite no previous exposure.
- *C. albicans* serotypes change with the progression of HIV disease from the A predominant biotype to serotype B, although the latter is found especially in homosexual men, irrespective of their HIV serostatus.
- Serotype B in particular appears resistant to flucytosine and fluconazole, although itraconazole may still be active.
- About 15% of candidiasis in HIV disease is due to non-*albicans* species, including:
 - *C. krusei*
 - *C. tropicalis*
 - *C. parapsilosis*
 - *C. lambica*
 - *C. kefyr*

- *Torulopsis glabrata*
- *Saccharomyces cerevisiae*.
- Infections with non-*albicans* species are increasing, coincident with increasing use of chronic antifungal therapy.
- *C. krusei* and *T. glabrata* particularly are becoming a problem since they are less likely to respond to fluconazole.
- New species closely related to *C. krusei*, such as *C. inconspicua*, are emerging and are fluconazole-resistant.
- New organisms, such as *C. dubliniensis*, related to *C. albicans*, have appeared, but at least at present remain largely fluconazole-sensitive.
- Up to 25% of HIV-infected patients with candidiasis have *C. albicans* plus other species.

Clinical features

See also Chapter 23.

- Thrush (pseudomembranous candidiasis) is one of the most obvious oral lesions in HIV infection and tends to be associated with lower CD4 counts, typically less than 200 cells/ml (see Fig. 40.3).
- Other types of candidiasis may also be seen, especially:
 - erythematous; indeed, this form of candidiasis may be a common early oral manifestation of HIV infection and presents as pink or red macular lesions, typically on the palate and dorsum of tongue and often mixed with white lesions (Fig. 40.6).
 - angular stomatitis (cheilitis)
 - median rhomboid glossitis
 - hyperplastic candidiasis.

Diagnosis

This is mainly clinical, supported by investigations discussed in Chapter 23.



Fig. 40.6 Erythematous candidiasis in HIV disease; a typical site is the vault of the palate

Management

Early treatment of oral candidiasis in HIV disease is warranted, not only because of the discomfort, but also because foci may act as reservoirs for spread, particularly to the oesophagus:

- Predisposing factors, such as smoking and xerostomia should be controlled first.
- Antiretroviral and protease inhibitor treatment of HIV infection may aid resolution.
- Antifungals; topical therapy of candidiasis with gentian violet, nystatin, amphotericin or clotrimazole is often successful initially within about 14 days, but relapses are common and these agents are not always palatable, or accepted by children. Failures are mainly attributable to underlying immunodeficiency and poor patient compliance due to:
 - polypharmacy
 - gastrointestinal upset
 - unpalatable taste of some agents
 - drug intolerance.
- Antifungal prophylaxis should also be considered. Antifungal resistance is now a significant clinical problem in HIV-infected persons, especially in intravenous drug users, even in patients who have received no fluconazole, since resistance may be transferred and fluconazole-resistant species may be transmitted between patients. Azole resistance appears to arise because of changes in fungal enzymes or permeability. Risk factors include:
 - severe immune defect
 - previous fluconazole use, especially intermittent or low-dose therapy. Fortunately, there may still be clinical response to fluconazole in fluconazole-resistant candidiasis, and amphotericin, ketoconazole and itraconazole may remain clinically effective. Therapy in fluconazole-resistant cases, therefore, includes: topical amphotericin or higher oral doses of fluconazole (200–600mg/day), fluconazole suspension as an oral rinse, ketoconazole (400 mg/day) or itraconazole (200–400mg/day). Voriconazole or caspofungin may be indicated.

Hairy leukoplakia

Hairy leukoplakia is a common, corrugated (or 'hairy') white lesion usually seen on the tongue mainly in HIV/AIDS and other immunocompromising states.

Hairy leukoplakia:

- may be associated with EBV
- typically affects the lateral margins of the tongue (Figs 40.7 and 40.8)
- produces a white lesion that is not removed by wiping with a gauze
- is not known to be premalignant



Fig. 40.7 Hairy leukoplakia

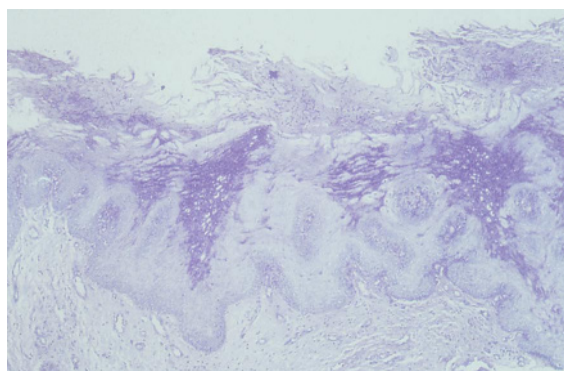


Fig. 40.8 Hairy leukoplakia histopathology

- is a predictor of bad prognosis
- may be associated with lymphoma elsewhere.

Diagnosis is largely clinical, supported by proof of EBV and usually HIV serotesting. Treatment is not often required, but the condition often resolves with aciclovir or other agents active against EBV, or with antiretroviral agents.

Kaposi sarcoma

Kaposi sarcoma (KS):

- arises from endothelial cells
- has been called 'gay cancer' by some since it is transmitted sexually especially to MSM, and seen rarely in HIV-infected children or haemophiliacs
- is caused by a newly identified virus HHV-8, which is transmitted sexually, often as a co-infection with HIV. Like all herpesviruses this is a DNA virus, which is seen more commonly where hygiene is poor, and remains latent after infection. It is found in saliva
- presents initially as asymptomatic red, blue or purple macules
- progresses to papules, nodules or ulcers and may become painful

- often involves the skin or mucosa in the head and neck
- is most common around the face (especially on the nose) and mouth
- occurs especially at the hard/soft palate junction or the anterior maxillary gingivae (see Fig. 40.4)

Diagnosis of KS must be supported by biopsy examination (see Fig. 40.5), since a clinically and histologically similar but distinct lesion caused by the bacterium *Bartonella (Rochalimaea) henselae* or *quintana* can cause a lesion, epithelioid angiomatosis, that responds well to antibiotics. Management of oral KS is often with intral-lesional injections of vinblastine, or systemic chemotherapy. KS responds badly to irradiation.

Lymphomas

Lymphomas are seen increasingly in AIDS and are often:

- non-Hodgkin's lymphomas
- part of widespread disease
- seen in the maxillary gingivae/faucet
- associated with EBV
- fairly resistant to therapy.

Diagnosis must be confirmed by biopsy examination. Management is with chemotherapy.

Gingival and periodontal disease

Necrotizing ulcerative gingivitis (Fig. 40.9) and periodontitis can be features of HIV infection, and typically these:

- occur disproportionately to the level of oral hygiene and plaque control
- are painful
- are localized
- cause rapid alveolar bone loss.

Diagnosis is clinical. The possibility of HIV/AIDS is heightened where there are additional suggestive lesions or where there is clear high risk of HIV infection, such as in an intravenous drug user. Management is with improved oral hygiene, debridement, chlorhexidine and sometimes metronidazole.

Mouth ulcers

Mouth ulcers may appear in HIV disease, but are, of course, common lesions in many non-HIV-infected persons. Ulcers may be unrelated to the HIV infection, or may be related to:

- aphthous-type ulcers, especially of the major type
- neoplasms, such as Kaposi sarcoma or lymphoma



Fig. 40.9 Necrotizing gingivitis in AIDS



Fig. 40.10 HPV and HSV in AIDS

- opportunistic pathogens, such as the herpesviruses (herpes simplex, varicella zoster, EBV, CMV), fungi (e.g. histoplasmosis or cryptococcosis), mycobacteria (e.g. tuberculosis or non-tuberculous mycobacteria (NTM)) or protozoa (e.g. leishmaniasis)
- drug use.

They may be part of widespread disease, such as disseminated cytomegalovirus infection, disseminated cryptococcosis or disseminated lymphoma, and thus the advice of a physician can be helpful if not mandatory. Diagnosis can be difficult and biopsy with microbial DNA studies may well be indicated. Management depends on the aetiology, but chlorhexidine and topical analgesics can be helpful. Antimicrobials or other specific therapies are often indicated to control the lesions, depending on the cause. Granulocyte colony stimulating factors or thalidomide may be helpful in aphthous-like non-specific ulceration.

Other orofacial lesions

A wide spectrum of other orofacial lesions can be seen in HIV/AIDS, including the following:

- Cervical lymph node enlargement, as part of persistent generalized lymphadenopathy.
- Chronic sinusitis, which may be related to bacterial or, increasingly, fungal pathogens, such as aspergillosis or zygomycosis.
- Parotitis and xerostomia (HIV-salivary gland disease), seen particularly in HIV-infected children. Cystic salivary lesions are increasingly recognized.
- HSV infections (Fig. 40.10).
- HPV infections, in particular genital warts (condyloma acuminata) in or around the mouth (Fig. 40.10).
- Cranial neuropathies, such as facial palsy, pain or sensory loss.

Websites

<http://www.cdcnpin.org>

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41 Iatrogenic disease

Key points

- Immunosuppression, chemotherapy, radiotherapy, transplantation and drugs can cause orofacial complications.
- Immunosuppression can result in virtually the same range of complications seen in people with HIV/AIDS.
- Chemo- or radiotherapy commonly cause mucositis, which can cause severe pain, interfere with quality of life, and be the portal for septicaemia.
- Radiotherapy can result in a range of complications including xerostomia, and caries, and osteo-radionecrosis (ORN), and loss of taste, which can interfere with quality of life.
- Transplantation can result in a range of complications including mucositis, infections and graft-versus-host disease.
- Drug adverse effects can damage any orofacial tissue.

Introduction

A number of medical and surgical treatments can result in iatrogenic disease affecting various orofacial tissues. The most dramatic effects are seen in patients on immunosuppressive therapy and those treated with cytotoxic agents or radiotherapy to the head and neck region. However, a surprisingly wide range of drugs can affect the orofacial tissues on occasion (see Ch. 45) and the astute diagnostician will always search the literature for such possibilities.

Immunosuppression

Immunosuppressive therapy is used especially to suppress:

- rejection in transplant recipients (bone marrow, kidney, liver, pancreas, heart and heart-lung); these are the most severely immunocompromised patients
- autoimmune disorders
- connective tissue diseases

- some malignant tumours, especially lymphoproliferative neoplasms.

A variety of drugs are used to induce immunosuppression, especially corticosteroids and calcineurin antagonists (such as ciclosporin, tacrolimus and sirolimus). Drugs such as azathioprine, cyclophosphamide and chlorambucil are cytotoxic to a range of cells, including some immunocytes, and are, therefore, also used for immunosuppression. A range of orofacial effects can arise (Box 41.1).

Infections

Patients on immunosuppressive agents are at risk from oral infections, which may be opportunistic (involving micro-organisms that are normally commensal) or may involve exogenous pathogens, and can include:

- fungal infections:
 - candidiasis (see Ch. 23)
 - *Aspergillus* spp. may infect the paranasal sinuses, palate or other sites by direct extension and haematogenously. Diagnosis is by demonstration of hyphae in a smear, serology and biopsy. Intravenous amphotericin may be effective
 - mucormycosis (zygomycosis: phycomycosis) is infection by *Mucor* or *Rhizopus* spp., mainly of the paranasal sinuses and nose of immunosuppressed or poorly controlled diabetic or leukaemic patients. Diagnosis is by biopsy and culture: treatment is by control of underlying disease, debridement and intravenous amphotericin
- mycobacterioses
- herpetic infections; antivirals, such as aciclovir by slow intravenous infusion or orally, repeated 8-hourly, or valacyclovir or famciclovir, are indicated for severe herpes simplex virus infections in immunocompromised patients

➤ Box 41.1

Orofacial effects possible in patients on immunosuppressive therapy

- Adverse effects:
 - infections
 - neoplasms
- Other effects, e.g. ciclosporin-induced gingival swelling

- odontogenic infections, which are potentially life threatening in the immunosuppressed patient, and broad-spectrum cover is needed (such as penicillin plus gentamicin).

Patients may also be at risk from attempts at treatment; thus, for example, broad-spectrum antibiotics used to control bacterial infections increase the hazard of fungal infections.

Neoplasms

Neoplasms, at least some of which are virally related, may also be a risk in chronic immunosuppression including:

- Kaposi sarcoma
- lymphoproliferative syndromes (post-transplant lymphoproliferative disease: PTLTD), which may appear late – even many years after transplantation – and range from hyperplastic-appearing lesions to non-Hodgkin's lymphoma or multiple myeloma. Reduction in immunosuppressives can often reverse PTLTD. Surgical resection, cytotoxics, anti-CD21 and anti-CD24 antibodies, interferon-alpha and rituximab have been effectively used for treatment
- squamous cell carcinomas of the skin and of the lip.

Chemotherapy

The oral adverse effects of chemotherapy can include (Box 41.2):

- mucositis – which may affect some two-thirds of patients
- infections – especially candidal, HSV and human papillomaviruses
- pain – related to mucositis or infections, or to drugs such as vinca alkaloids and doxorubicin
- bleeding – thrombocytopenia increases the liability to gingival and oral bleeding
- xerostomia.

Mucositis

Mucositis is the term given to widespread oral erythema, ulceration and soreness, common after chemo- or radiotherapy.

Incidence

Mucositis is a common complication of a number of procedures involving chemo-, radio- or chemoradiotherapy.

► Box 41.2

Orofacial effects possible in patients on cytotoxic chemotherapy

- Adverse effects:
 - mucositis
 - bleeding
- Other effects, e.g. infections

Age

It can occur at any age.

Sex

It can affect both genders.

Aetiology and pathogenesis

Mucositis can arise as a consequence of the:

- direct effect of the interventional regimen on cell division
- oral infections that may ensue
- release of cytokines (such as interleukin-1 and tumour necrosis factor- α)
- aggravation by trauma.

Mucositis is seen especially with:

- cisplatin
- etoposide
- fluorouracil
- melphalan.

Also with:

- doxorubicin
- methotrexate
- taxanes
- vinblastine.

Less with:

- asparaginase
- carmustine.

Clinical features

Mucositis presents with:

- pain
- erythema



Fig. 41.1 Mucositis

- ulceration (Fig. 41.1)
- sometimes bleeding.

Mucositis can lead to a number of problems, including:

- significantly interfering with quality of life
- acting as a portal for septicaemia, especially streptococcal, sometimes with lethal consequences
- extending hospitalization
- increasing costs of care.

Diagnosis

Diagnosis of mucositis is clinical and it is helpful to score the degree in order to monitor progression and therapy. The World Health Organization toxicity grading was one of the first mucositis scales used but several are now available (Box 41.3).

Management

Discomfort from established mucositis can be reduced by (Box 41.4):

- opioids, such as morphine and hydromorphone
- avoiding irritants (smoking, spirits or spicy foods)
- good oral hygiene. Many suggest toothbrushing should be avoided during the first week
- oral cooling using ice chips
- topical analgesics may help to combat pain and dysphagia when used prior to meals. These include:
 - benzydamine hydrochloride used prior to meals
 - 2% lidocaine (lignocaine) solution mouthwash
 - aspirin

► Box 41.3

WHO mucositis scale

Grade	Clinical features
0	–
1	Soreness/erythema
2	Erythema and ulcers – but able to eat solids
3	Ulcers – but requires liquid diet
4	Oral alimentation not possible

► Box 41.4

Management of oral complications of chemotherapy

Complication	Management
Mucositis	Prophylaxis: oral cooling using ice chips 30 minutes for 5-fluorouracil 20 minutes for edatrexate
Pain	Opioids, benzydamine hydrochloride used prior to meals 2% lidocaine (lignocaine) solution mouthwash
Candidiasis	Nystatin suspension 100 000 IU/ml as mouth wash four times daily Fluconazole if immunocompromised

Modified from Rubenstein et al 2004

- growth factors may speed recovery; those used include:
 - keratinocyte growth factor mainly, but also
 - granulocyte colony stimulating factor
 - granulocyte-macrophage colony stimulating factor
 - epidermal growth factor
 - transforming growth factor.

Patients on chemotherapy may also suffer a range of other problems (Box 41.5).

Radiotherapy to the head and neck region

Radiation produces free radicals from intracellular water:

- Free radicals damage DNA and mitosis
- Irradiated cells undergo death on mitosis.

Relevant and other systemic disorders

Radiotherapy damages mucosa after 12 days, skin after 21 days and also damages endothelium after 60 days, but the damage affects only cells undergoing mitosis:

- Epithelium undergoes frequent mitoses
- Bone only undergoes mitosis after trauma.

Radiotherapy can cause a range of adverse effects (Box 41.6). Some arise immediately and are predictable – notably

mucositis and xerostomia – whilst others appear later and unpredictably.

Immediate complications

Mucositis is invariable where radiation involves the oral mucosa, but can be reduced by (Box 41.7):

- minimizing doses and field of radiation
- using mucosa-sparing blocks
- using amifostine before therapy
- betamethasone mouthwashes.

► Box 41.5

Systemic effects possible in patients on chemotherapy

- Cardiotoxicity
- Renal failure
- Pulmonary fibrosis
- Myelosuppression
- Alopecia
- Nausea
- Vomiting
- Diarrhoea
- Cystitis
- Sterility
- Myalgia
- Neuropathy
- Local reactions
- Phlebitis

► Box 41.6

Orofacial effects possible in patients on radiotherapy

- Adverse effects
- Mucositis
- Xerostomia:
 - taste loss
 - caries
 - candidiasis
 - sialadenitis
- Osteoradionecrosis
- Trismus

► Box 41.7

Management of oral complications of radiotherapy

Complication	Management
Mucositis	Prophylaxis: amifostine 200 mg/m ² /day; betamethasone mouthwash four times daily from the day before radiotherapy, throughout the course
Xerostomia	Saliva substitute* Frequent ice cubes, popsicles or sips of water Sialogogues, e.g. pilocarpine or cevimeline
Osteoradionecrosis/irradiation-induced	Avoid by atraumatic extractions under antibiotic cover, with primary wound closure Planned pre-radiotherapy extractions or extractions within 3 months of radiotherapy
Loss of taste	Consider zinc sulphate
Trismus	Jaw-opening exercises three times daily
Candidiasis	Nystatin suspension 100 000 IU/ml as mouth wash four times daily Fluconazole or itraconazole if immunocompromised
Caries	Daily topical fluoride applications: high fluoride-containing toothpastes Avoid sugary diet
Dental hypersensitivity	Fluoride applications/mouthwashes

*Artificial saliva (e.g. methylcellulose) or mucin



Fig. 41.2 Xerostomia



Fig. 41.3 Radiation caries

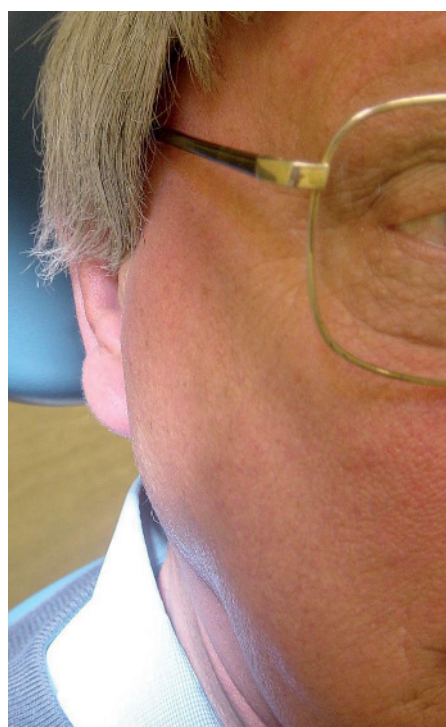


Fig. 41.4 Acute sialadenitis

The time to healing depends on the radiation dose intensity, but is usually complete within 3 weeks after the end of treatment. Tobacco smoking delays resolution:

- Salivary changes: xerostomia (Fig. 41.2), which predisposes to caries (Fig. 41.3), candidiasis and bacterial acute ascending sialadenitis (Fig. 41.4) (see Ch. 43). Changes may be:
 - quantitative (dry mouth or xerostomia)
 - qualitative (pH falls; buffering capacity decreases; electrolytes change).
- Factors predisposing to salivary changes include:
 - radiation
 - dose
 - fraction size and number of exposures
 - type
 - salivary gland
 - function before radiotherapy
 - volume irradiated.

Longer-term complications:

- Caries can rapidly progress, and affect areas usually not predisposed, such as incisal edges, smooth surfaces, and the lower incisor as well as other areas.

- Trismus arises because of reduced vascularity from the endarteritis obliterans following radiotherapy (Fig. 41.5) leading to fibrosis in the muscles of mastication and surrounding tissues.
- Osteoradionecrosis (ORN) is potentially the most serious complication and follows endarteritis obliterans.
- The mandible, a compact bone with high density and poor vascularity, is more prone than the maxilla to ORN.
- ORN risk is greatest:
 - when radiation dose exceeds 60 Gy
 - from 10 days before to several years after radiotherapy
 - at 3–12 months after radiotherapy
 - in the malnourished or immunoincompetent.
- The initiating factor is often trauma, such as tooth extraction, or oral infection or ulceration from an appliance.
- Presentation is of exposed bone in an irradiated mouth, with or without external sinuses, pain and pathological fracture.
- Treatment is by long-term antibiotics, especially tetracycline (which has high bone penetrance), and local cleansing; hyperbaric oxygen may assist.
- Loss of taste.
- Cervical atherosclerosis.

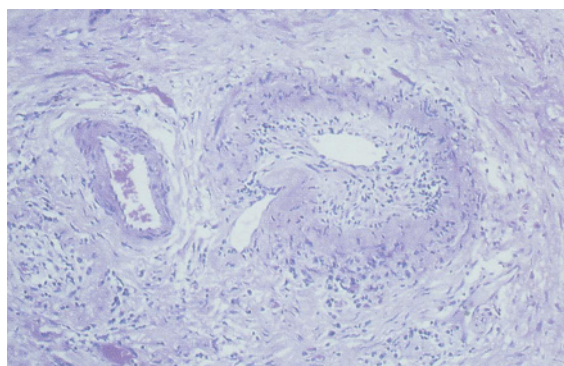


Fig. 41.5 Radiation-induced endarteritis obliterans

► Box 41.8

Orofacial complications of cancer therapy

Therapy	Oral complications
Radiotherapy	Pain, mucositis, xerostomia, candidiasis, caries, sialadenitis, osteoradionecrosis and fibrosis
Chemotherapy	Pain, mucositis, xerostomia, candidiasis, herpesviruses and neuropathy
Surgery	Pain, neuropathy, disfigurement, impaired speech and swallowing

Chemoradiotherapy

Drugs may act as radiosensitizers, and increase the mucositis produced by radiotherapy. This is seen especially with regimens involving:

- cisplatin and fluorouracil
- cisplatin, epirubicin and bleomycin
- carboplatin.

Cancer therapy

See Chapter 22 and Box 41.8.

Transplantation

Orofacial complications can follow transplantation of solid organs or bone marrow [human precursor cell transplantation (HPCT) or haematopoietic stem cell transplantation (HSCT)]. These are largely as a consequence of the immunosuppressive agents used.

Solid organ transplantation

Immunosuppressive therapy is universally used after transplantation, with the potential problems outlined above.

Haematopoietic stem cell transplantation

HSCT is increasingly used to treat:

- congenital metabolic diseases
- congenital immune diseases
- haematological malignancies (aplastic anaemia, leukaemias, lymphomas)
- solid malignancies.

The procedure of HSCT involves the recipient receiving:

- ablation of bone marrow cells by high-dose chemotherapy with drugs such as cyclophosphamide
- total (whole) body irradiation (TBI)
- transfusion of bone marrow aspirate from a donor who has been stimulated with growth factors.

This regimen results in:

- profound immunosuppression until the donor bone marrow graft takes and, therefore, patients are isolated to reduce the risk of infections
- graft-versus-host disease (GVHD) in about 60% of cases; this can produce further immune defects and is potentially lethal
- lymphoproliferative syndromes [post-transplant lymphoproliferative disorder (PTLD)] and lymphomas (see below) in rare patients.

Oral complications of HSCT

Oral complications are common and can be a major cause of morbidity from the effects of the underlying disease, chemo- or radiotherapy, or GVHD and include:

- mucositis – this typically begins around 5 days post-HSCT, but by around 9–14 days post-HSCT basal cells regenerate and it resolves. Apart from the measures discussed above, it may be ameliorated by use of glutamine and interleukin-11
- ulceration – mainly a consequence of granulocytopenia, this resolves by around 9–14 days post-HSCT, when the neutrophils rise >500 cells/ml
- xerostomia
- bleeding

- Infections – superficial infections are frequent and can involve a wide range of infections, mainly
- herpes simplex virus (HSV): about 60% of patients secrete HSV orally within 50 days, and many have lesions, such as ulcers
- cytomegalovirus (CMV): about 60% of patients secrete CMV between days 30 and 150 and lesions, such as ulcers, may result
- varicella-zoster virus: 40% are infected within 6 months and 80% develop zoster
- Epstein-Barr virus (EBV): about 60% secrete EBV and, although uncommon, hairy leukoplakia or lymphoproliferative disease may result
- human papilloma viruses (HPV): can cause extensive lesions over the 3–8 months post transplant
- candidiasis: carriage and oral lesions are almost invariable in the absence of prophylactic antifungal therapy
- mucormycosis; a rare, but serious complication
- septicaemia is less common, but bacterial infections involving viridans Streptococci, Enterococci, *Leptotrichia buccalis* and Gram-negative organisms may arise. From 25% to 75% of septicaemias arise from the oral cavity.

Graft-versus-host disease

GVHD arises as the graft mounts a damaging immune response against the recipient and prolongs the oral ulceration/mucositis. Acute GVHD appears between 10 and 100 days post transplant, and is seen in about 60% of transplant survivors. Chronic GVHD occurs after 100 days post-HSCT and affects around 50% of patients after HSCT, may follow acute GVHD, or may arise *ab initio*.

Acute GVHD

Acute GVHD affects mainly the liver, gastrointestinal tract and mucocutaneous tissues, and can be lethal: prophylactic immunosuppressive therapy usually using methotrexate and ciclosporin is therefore used for the first 100 days post-HSCT to try to prevent GVHD.

The oral manifestations of acute GVHD are difficult or impossible to differentiate from chemotherapy-induced mucositis and consist of:

- painful mucosal desquamation and ulceration. Erythema and ulceration are most pronounced at 7–11 days after HSCT, and may be associated with obvious infection. Small white lesions affect the buccal and lingual mucosa early on, but clear by day 14. The ventrum of the tongue, buccal and labial mucosa and gingiva may be affected
- cheilitis
- xerostomia; most significant in the first 14 days after transplantation and a consequence of drug treatment and/or irradiation



Fig. 41.6 Lichenoid lesions in graft-versus-host disease (GVHD)



Fig. 41.7 Early lesions of ciclosporin-induced gingival swelling appearing on the interdental papillae

- infections; candidiasis is common, as is HSV stomatitis (occasionally zoster), CMV, protozoal and Gram-positive bacterial infections
- oral purpura and bleeding.

Acute GVHD is treated with high-dose immunosuppressive therapy.

Chronic GVHD

Chronic GVHD is severe and involves multiple organs, mainly the liver, gastrointestinal tract, eyes and mucocutaneous tissues including, in 80% of cases, the mouth.

The oral lesions in chronic GVHD are coincident with skin lesions, and include:

- generalized mucosal erythema
- lichenoid lesions (Fig. 41.6)
- ulceration
- xerostomia, salivary gland atrophy and taste abnormalities
- infections, especially candidiasis
- hairy leukoplakia

- sclerodermatous syndrome
- ciclosporin may induce gingival swelling (Fig. 41.7).

Diagnosis of GVHD is from the history and clinical features and a mucosal or labial salivary gland biopsy, which shows mononuclear cell infiltrates. GVHD is treated with high-dose immunosuppressive therapy. Management of GVHD oral lesions is best with use of:

- oral hygiene measures
- analgesics (morphine or hydromorphone)
- topical azathioprine or ciclosporin
- non-alcoholic chlorhexidine mouth rinses
- nystatin mouth washes (5000 000 units) or fluconazole
- pilocarpine
- xylitol chewing gum
- artificial saliva
- growth factors.

Drug adverse reactions

Drugs can sometimes give rise to a number of adverse orofacial manifestations, particularly salivary changes – notably xerostomia, but also taste disturbances, burns, oral ulceration, cheilitis, pigmentation, swelling (see also Ch. 29), pain and neuropathies, and/or effects on the hard tissues (teeth and jaws).

The opportunistic infections secondary to cytotoxic chemotherapy and increased prevalence of dysplastic and malignant lip and oral lesions in immunosuppressed patients are discussed above. The importance of tobacco, alcohol and betel as risk factors for leukoplakia and oral epithelial dysplasia is discussed in Chapters 22 and 27. Sanguinarine, the principal alkaloid of the blood-root plant (*Sanguinaria canadensis*), which is used in some mouthwashes and dentifrices for its anti-plaque activity, may be associated with the development of oral leukoplakia.

Salivary changes

Xerostomia

Drugs are the most common cause of reduced salivation (see Box 45.1) and the xerostomia can be treated by reducing drug doses or stimulating salivation with a cholinergic agent.

Salivary gland swelling or pain

Some drugs may cause salivary gland swelling or pain (see Box 45.2).

Sialorrhoea

Anticholinesterases are the main cause of sialorrhoea (see Box 45.3).

Taste abnormalities

Drugs commonly cause taste acuity loss (hypogeusia) or distortion (dysgeusia) either by interfering in the chemical composition or flow of saliva, or affecting taste receptor function or signal transduction (see Box 45.4). Drugs causing xerostomia can affect taste.

Burns

Burns may follow the accidental ingestion of caustics, such as lime, the local application of aspirin or toothache preparations, potassium tablets, pancreatic supplements and other agents, such as trichloroacetic acid or hydrogen peroxide, or from the use of various oral healthcare products. Sodium lauryl sulfate, present in some oral healthcare products, particularly dentifrices, may cause mucosal irritation or ulceration. Cocaine use may cause burns.

Ulceration

Aphthous-like ulceration may follow the use of NSAIDs and other drugs (see Box 45.5).

Mucositis

Cytotoxic drugs are commonly associated with mucositis (see Box 45.5). Methotrexate, 5-fluorouracil, doxorubicin, melphalan, mercaptopurine or bleomycin are particularly implicated.

Fixed drug eruptions

Fixed drug eruptions (contact stomatitis or stomatitis venenata) comprise repeated ulceration at the same site in response to a particular drug (see Box 45.6). The lesions may be localized to the mouth or can be associated with lesions at other mucocutaneous sites, and manifest as ulceration, bullae, erythematous patches or superficial erosions. Initially the lesions are solitary, but with repeated drug exposure they may become multiple.

Lichenoid eruptions

Since the advent of antimalarial therapy there have been an ever-increasing list and spectrum of drugs that may give rise to mucocutaneous lichen planus (LP)-like eruptions (lichenoid reactions) (see Box 45.7).

The most reliable means to diagnose lichenoid reactions is if the reaction remits with drug withdrawal and returns on rechallenge, but frequently this is not possible because of the need to ensure patient safety.

Pemphigoid and other bullous disorders

At least 30 drugs can give rise to bullous or mucous membrane pemphigoid (see Box 45.8).

Pemphigus

Several drugs can give rise to pemphigus (see Box 45.9).

Erythema multiforme

A wide range of drugs may give rise to erythema multiforme or toxic epidermal necrolysis (see Box 45.10).

Lupus-like (lupoid) disorders

See Box 45.11.

Contact cheilitis

Cheilitis is commonly caused by contact reactions to cosmetics or foods, but drugs may also be implicated (see Box 45.12).

Discolouration and pigmentation

Superficial transient discolouration of the dorsum of the tongue and other soft tissues and teeth may be of various colours, typically yellowish or brown and may be caused by some foods and beverages (such as coffee and tea), habits (such as tobacco, betel and crack cocaine use), and some drugs.

Blue, blue-grey or brown intrinsic mucosal pigmentation can be an adverse effect of drugs (see Box 45.13). Localized areas of pigmentation of the mucosa may be due to amalgam, while gingival pigmentation secondary to the gold or metal alloys of crowns can arise. Heavy metal salts were previously reported to cause pigmentation, particularly of the gingival margin.

Kaposi's sarcoma of the mouth is a rare complication of immunosuppression, manifesting as a blue, red or purple macule, papule, nodule or area of ulceration, typically on the palate or gingivae, but can affect other oral mucosal sites (see Ch. 39).



Fig. 41.8 Tetracycline staining

Swelling

- Gingival swelling (see Ch. 29)
- Gingival enlargement is a well described oral side-effect of drug therapy (see Box 45.14).
- Lip and mucosal swelling
- Angioedema may be drug-related (see Box 45.15).

Trigeminal neuropathies

- Drugs occasionally induce neuropathies (see Box 45.16).
- Involuntary facial movements.
- Psychoactive drugs in particular can induce abnormal facial movements (see Box 45.17).
- Orofacial pain and dysaesthesia.
- Vinca alkaloids are well recognized as causing pain (see Box 45.19).

Effects on teeth

Tooth discolouration

Some drugs are able to produce alterations in the colour of the teeth, usually by superficial staining (see Boxes 45.20–45.22). Tetracycline intrinsic staining of the teeth may be seen if tetracyclines are given to pregnant or nursing mothers, when they can cause brown discolouration of the developing dentition, or when given to children under the age of 12 years (Fig. 41.8).

Alteration to tooth sensitivity

External tooth bleaching using hydrogen peroxide or carbamide peroxide (which releases hydrogen peroxide) can produce tooth sensitivity (see Box 45.23).

Osteochemonecrosis

Bisphosphonates, such as pamidronate and zoledronate, in particular when used intravenously in patients with bone metastases, can lead to painful refractory jaw bone exposures (sometimes termed osteochemonecrosis or osteonecrosis of the jaws; ONJ). A few cases have followed the use of oral bisphosphonates, such as alendronate. Osteochemonecrosis presents with painful, exposed, necrotic bone, most commonly in the mandible. Oral surgery (exodontia, periodontal surgery, endodontal surgery and endosseous implants) can be precipitants. Osteochemonecrosis may develop after as few as 4 months of bisphosphonate therapy.

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42

Oral manifestations of disorders of specific systems

This chapter annotates the orofacial manifestations of disorders of specific systems: further details can be found elsewhere in this book.

► Box 42.1

Cardiovascular disease

Angina pectoris

- Pain referred to jaw rarely

Anticoagulants

- Bleeding tendency

Giant cell arteritis (cranial or temporal arteritis)

- Pain usually over the temple
- Rarely, tongue pain or ischaemic necrosis

Hereditary haemorrhagic telangiectasia

- Telangiectasias that may bleed profusely

Hypertension (problems caused by some antihypertensive agents)

- Dry mouth
- Gingival swelling (nifedipine)
- Lichenoid lesions (methyldopa, ACE inhibitors)
- Angioedema (ACE inhibitors)
- Burning mouth (ACE inhibitors)

Ischaemic heart disease

- Arterial calcifications on orthopantomogram
- Possibly periodontitis

Polyarteritis nodosa

- Ulcers

Shunts: right to left (e.g. Fallot's tetralogy)

- Cyanosis
- Delayed tooth eruption

► Box 42.2

Connective tissue disease

Any connective tissue disease

- Sjögren syndrome
- Lymph node enlargement
- Facial sensory loss

Ehlers–Danlos syndrome

- Temporomandibular joint hypermobility
- Pulp stones
- Periodontitis rarely

Felty syndrome

- Temporomandibular arthritis
- Sjögren syndrome
- Drug reactions (e.g. lichenoid)
- Ulcers

Lupus erythematosus

- White lesions
- Ulcers
- Sjögren syndrome

Mixed connective tissue disease

- Ulceration

- Pain
- Sjögren syndrome

Rheumatoid arthritis

- Temporomandibular arthritis
- Sjögren syndrome
- Drug reactions (e.g. lichenoid)

Still syndrome

- Temporomandibular arthritis
- Sjögren syndrome
- Ankylosis

Systemic sclerosis

- Stiffness of lips, tongue, etc.
- Trismus
- Telangiectasia
- Sjögren syndrome
- Periodontal ligament widened on radiography
- Mandibular resorption
- Oral cancer

► Box 42.3

Endocrine conditions

Acromegaly

- Spaced teeth
- Mandibular prognathism
- Macroglossia

Diabetes mellitus

- Periodontal disease, accelerated
- Xerostomia
- Candidiasis
- Sialosis
- Lichen planus
- Oral cancer

Gigantism

- Spaced teeth
- Mandibular prognathism
- Macroglossia
- Megadontia

Hyperparathyroidism

- Giant cell granulomas
- Loss of lamina dura
- Osteitis fibrosa cystica, rarely

Hypoadrenocorticism

- Mucosal hyperpigmentation

Hypoparathyroidism (congenital)

- Dental hypoplasia
- May be chronic candidiasis if there is associated immune defect

Hypopituitarism (congenital)

- Microdontia
- Retarded tooth eruption

Hypothyroidism (congenital)

- Macroglossia
- Retarded tooth eruption

Menopause

- Osteoporosis

Precocious puberty

- Accelerated tooth eruption (fibrous dysplasia in Albright syndrome)

Pregnancy

- Gingivitis
- Epulis

► Box 42.4

Gastrointestinal disorders

Chronic pancreatitis

- Sialosis rarely

Coeliac disease

- Ulcers
- Glossitis
- Angular stomatitis
- Dental hypoplasia in severely affected children

Crohn's disease

- Facial or lip swelling
- Mucosal tags
- Gingival hyperplasia
- Cobblestoning of mucosa
- Ulcers
- Glossitis
- Angular stomatitis

Cystic fibrosis

- Salivary gland swelling

Gardner syndrome (familial colonic polyps)

- Osteomas

Gastric regurgitation

- Tooth erosion
- Halitosis

Malabsorption syndromes

- Ulcers
- Glossitis
- Angular stomatitis
- Sialosis

Patterson–Kelly syndrome

- Oral cancer

Pancreatic cancer

- Periodontitis

Pernicious anaemia

- Ulcers
- Glossitis
- Angular stomatitis

Peutz–Jeghers syndrome (small intestinal polyps)

- Melanosis

► Box 42.5

Haematological disorders

Aplastic anaemia

- Ulcers
- Bleeding tendency

Graft-versus-host disease

- Lichenoid lesions
- Dry mouth

Haematinic – iron, folic acid or vitamin B₁₂ deficiency

- Burning mouth sensation
- Glossitis
- Ulcers
- Angular cheilitis

Haemolytic disease of newborn

- Pigmentation
- Rarely, enamel defects

Haemopoietic stem cell transplantation

- Ulcers
- Mucositis
- Xerostomia
- Graft-versus-host disease

Hypereosinophilic syndrome

- Ulceration

Hypoplasminogenaemia

- Gingival swelling and ulceration

Leukaemia

- Infections
- Ulcers
- Bleeding tendency
- Gingival swelling in myelomonocytic leukaemia
- Cervical lymph node enlargement
- Labial sensory loss

Leucocyte defects

- Infections, especially herpetic and candidal
- Ulcers

Lymphoma

- Infections
- Ulcers
- Swelling
- Cervical lymph node enlargement

Multiple myeloma

- Bone pain
- Tooth mobility
- Amyloid

Myelodysplastic syndrome

- Ulcers
- Labial sensory changes

Sickle cell anaemia

- Jaw deformities caused by marrow expansion
- Rarely, osteomyelitis or pain

Thalassaemia major

- Jaw deformities caused by marrow expansion

Thrombocytopenia

- Bleeding tendency
- Purpura

Immunodeficiencies

- See below for HIV

Ataxia telangiectasia

- Recurrent sinusitis
- Ulceration
- Facial and oral telangiectasia
- Cervical lymphomata
- Mask-like facial expression

Chédiak–Higashi syndrome

- Cervical lymph node enlargement
- Ulceration
- Periodontitis

Chronic benign neutropenia

- Ulceration
- Severe periodontitis

Chronic granulomatous disease

- Cervical lymph node enlargement and suppuration
- Candidiasis (including CMC*)
- Enamel hypoplasia
- Acute gingivitis
- Ulceration

Cyclic neutropenia

- Ulceration
- Severe periodontitis
- Eczematous lesions of the face

Common variable immunodeficiency

- Recurrent sinusitis
- Candidiasis (including CMC*)

Di George syndrome (CATCH22)

- Abnormal facies
- Candidiasis (including CMC*)
- Viral infections
- Bifid uvula
- Dental hypoplasia

Hereditary angioedema

- Swellings of face, mouth and pharynx

Job syndrome

- Abnormal facies

Lazy leucocyte syndrome

- Periodontitis
- Myeloperoxidase deficiency
- Candidiasis (including CMC*)

Continued

► Box 42.5

Haematological disorders—cont'd

Papillon-Lefevre syndrome

- Periodontitis

Selective IgA deficiency

- Tonsillar hyperplasia
- Ulceration
- Viral infections
- Parotitis

Severe combined immunodeficiency (SCID)

- Candidiasis (including CMC*)
- Viral infections
- Ulceration
- Absent tonsils
- Recurrent sinusitis

*Chronic mucocutaneous candidiasis

Sex-linked agammaglobulinaemia

- Cervical lymph node enlargement
- Ulceration
- Recurrent sinusitis
- Absent tonsils

Wiskott-Aldrich syndrome

- Candidiasis
- Viral infections
- Purpura

► Box 42.6

Immunological disorders

See also connective tissue disorders, and skin diseases

Angioedema

- Facial swelling

Behçet syndrome

- Ulcers

Graft-versus-host disease

- Lichenoid lesions
- Sicca syndrome
- Infections

Kawasaki disease (mucocutaneous lymph node syndrome)

- Cervical lymph node
- Enlargement
- Sore tongue
- Cheilitis

Langerhans histiocytoses (histiocytosis X)

- Loosening of teeth
- Jaw radiolucencies

Myasthenia gravis and other myopathies

- Facial weakness
- Lingual weakness
- Dysarthria

Reiter syndrome

- Ulcers
- Lesions like erythema migrans

Sarcoidosis

- Xerostomia
- Salivary gland swelling
- Heerfordt syndrome (parotid swelling, lacrimal swelling, facial palsy)
- Oral swellings

Sweet syndrome

- Ulcers

Wegener's granulomatosis

- Gingival swellings
- Ulcers

► Box 42.7

Infectious diseases

Aspergillosis

- Antral infections

Candidiasis

- White lesions
- Red lesions
- Angular stomatitis

Cat-scratch disease

- Lymph node enlargement

Coxsackie viruses

- Ulcers in herpangina and in hand, foot and mouth disease

Cryptococcosis

- Ulcers

Cytomegalovirus

- Ulcers
- Sialadenitis

ECHO viruses

- Ulcers in herpangina and in hand, foot and mouth disease

Epstein–Barr virus (in infectious mononucleosis)

- Sore throat
- Tonsillar exudate
- Palatal petechiae
- Cervical lymph node enlargement
- Ulcers
- Lymphoma
- Sialadenitis
- Recurrent parotitis, possibly in children
- Facial palsy

Gonorrhoea

- Pharyngitis
- Gingivitis
- Temporomandibular arthritis

Hepatitis C (see Box 42.8)

Herpes simplex

- Ulcers in primary infection
- Gingivitis in primary infection
- Vesicles on lips in recurrence (rarely, oral ulcers)
- Lymph node enlargement
- Facial palsy
- Erythema multiforme

Herpes zoster-varicella

- Ulcers in chicken pox, or in zoster of trigeminal maxillary or mandibular divisions
- Pain in maxillary or mandibular zoster
- Facial palsy in Ramsay–Hunt syndrome of zoster of the geniculate ganglion

Human herpesvirus-8

- Kaposi sarcoma

Histoplasmosis

- Ulcers

HIV (human immunodeficiency virus causing AIDS)

- Lymph node enlargement
- Infections, particularly herpetic and candidal
- Ulcers
- Kaposi sarcoma
- Lymphoma
- Hairy leukoplakia
- Parotitis
- Xerostomia
- Periodontitis
- Cranial nerve lesions
- Purpura

Leprosy

- Cranial nerve palsies

Lyme disease

- Facial palsy

Measles

- Koplik's spots

Mucormycosis

- Antral infections

Mumps

- Salivary gland swelling

Papilloma viruses

- Warts
- Papillomas
- Condyloma acuminata
- Focal epithelial hyperplasia

Paracoccidioidomycosis

- Ulcers

Rubella

- Palatal petechiae
- Dental hypoplasia in congenital rubella

Syphilis

- Chancre
- Mucous patches
- Ulcers
- Gumma
- Pain from neurosyphilis
- Leukoplakia
- Lymph node enlargement
- Hutchinson's teeth in congenital syphilis

Toxoplasmosis

- Cervical lymph node enlargement

Tuberculosis (including atypical mycobacteria)

- Ulcers rarely
- Cervical lymph node enlargement

► Box 42.8

Liver disorders

Alcoholic cirrhosis

- Bleeding tendency
- Sialosis

Biliary atresia

- Dental hypoplasia
- Pigmented teeth

Chronic active hepatitis

- Lichen planus

Hepatitis C

- Salivary swelling and xerostomia
- Lichen planus

Jaundice

- Bleeding tendency
- Jaundice

Kernicterus

- Dental hypoplasia
- Pigmented teeth

Primary biliary cirrhosis

- Sjögren syndrome
- Lichen planus

Transplants

- Infections
- Neoplasms
- Gingival swelling

► Box 42.9

Metabolic disorders

Amyloidosis

- Macroglossia
- Purpura

Erythropoietic porphyria

- Reddish teeth
- Bullae/erosions
- Dental hypoplasia

Folic acid deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

Hypophosphataemia

- Dental hypoplasia
- Large pulp chambers

Hypophosphatasia

- Loosening and loss of teeth (hypoplastic cementum)

Iron deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

Lesch–Nyhan syndrome (congenital hyperuricaemia)

- Self-mutilation

Mucopolysaccharidosis

- Spaced teeth
- Retarded tooth eruption
- Temporomandibular joint anomalies
- Enamel defects
- Cystic lesions

Neimann–Pick disease

- Retarded tooth eruption
- Loosening of teeth
- Mucosal pigmentation

Rickets (vitamin D dependent)

- Dental hypoplasia
- Large pulp chambers

Scurvy

- Gingival swelling
- Purpura
- Ulcers

Tangier disease

- Orange tonsillar deposits

Vitamin B₁₂ deficiency

- Burning mouth syndrome
- Ulcers
- Glossitis
- Angular cheilitis

► Box 42.10

Neurological disorders

Bulbar palsy

- Fasciculation of tongue

Cerebral palsy

- Spastic tongue
- Dysarthria
- Attrition

Cerebrovascular disease

- Facial palsy

Choreoathetosis

- Green staining of teeth in kernicterus

Disseminated sclerosis

- Pain
- Sensory loss
- Facial palsy

Down syndrome

- Delayed tooth eruption
- Macroglossia
- Scrotal tongue
- Maxillary hypoplasia
- Anterior open bite
- Hypodontia
- Periodontal disease
- Cheilitis

Epilepsy

- Trauma to teeth/jaws/mucosa
- Gingival swelling if on phenytoin

Facial palsy

- Palsy and poor natural cleansing of mouth on same side

Neurosyphilis

- Pain rarely
- Dysarthria
- Tremor of tongue

Parkinsonism

- Drooling
- Tremor of tongue

Riley-Day syndrome

- Self-mutilation
- Prominent fungiform papillae
- Salivary swelling
- Sialorrhoea

Stroke

- Periodontitis

Trigeminal neuralgia

- Pain

► Box 42.11

Psychiatric disorders

Anxiety states

- Dry mouth
- Cheek biting
- Bruxism

Bulimia

- Tooth erosion

Depression, hypochondriasis and various psychoses

- Dry mouth
- Discharges
- Pain
- Disturbed taste
- Disturbed sensation
- Artefactual ulcers
- Exfoliative cheilitis
- Bruxism

Drug abuse

- Oral burns
- Bruxism
- Oral neglect
- HIV/AIDS

Munchausen syndrome

- Self-mutilation
- Feigned dental disease

► Box 42.12

Renal disorders

Chronic renal failure

- Xerostomia
- Halitosis/taste disturbance
- Leukoplakia
- Dental hypoplasia in children
- Renal osteodystrophy
- Bleeding tendency

Dialysis

- Xerostomia
- Sialadenitis

Nephrotic syndrome

- Dental hypoplasia

Post-renal transplantation

- Infections, particularly herpetic and candidal
- Bleeding tendency
- Gingival swelling if on ciclosporin or nifedipine

Renal rickets (vitamin D resistant)

- Delayed tooth eruption
- Dental hypoplasia
- Enlarged pulp

► Box 42.13

Respiratory disorders

Asthma

- Candidiasis
- Caries

Bronchiectasis

- Dry mouth
- Malodour

Chronic obstructive airways diseases

- Cyanosis

Kartagener syndrome

- Sinusitis

Pneumonia

- Periodontitis

► Box 42.14

Skeletal disorders

Cherubism

- Jaw swellings

Cleidocranial dysostosis (dysplasia)

- Delayed tooth eruption
- Multiple supernumerary teeth
- Dentigerous cysts
- Short tooth roots

Craniofacial dysostosis (Crouzon syndrome)

- Maxillary hypoplasia
- Cleft palate

Fibrous dysplasia

- Expansive jaw lesions

Mandibulofacial dysostosis (Treacher–Collins syndrome)

- Cleft palate
- Mandibular hypoplasia

Osteogenesis imperfecta

- Dentinogenesis imperfecta in some

Osteopetrosis (Albers–Schonberg disease)

- Cranial neuropathies
- Delayed tooth eruption
- Osteomyelitis after tooth extractions

Osteoporosis

- Jaw osteoporosis
- Bisphosphonate osteochemonecrosis

Paget's disease

- Expansive jaw lesions
- Hypercementosis
- Osteomyelitis rarely after tooth extractions
- Post-extraction bleeding

► Box 42.15

Skin diseases

Acanthosis nigricans

- Papillomas

Chronic bullous disease of childhood

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Darier's disease

- White lesions

Dermatitis herpetiformis

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Ectodermal dysplasia

- Hypodontia
- Dental anomalies (peg-shaped teeth)
- Dry mouth

Ellis-van Creveld syndrome (chondroectodermal dysplasia)

- Multiple fraeni
- Short roots
- Hypodontia

Epidermolysis bullosa

- Blisters
- Erosions
- Scarring
- Dental hypoplasia

Erythema multiforme

- Ulcers
- Blood-stained crusting of lips

Lichen planus

- White lesions
- Red lesions
- Erosions
- Desquamative gingivitis

Linear IgA disease

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Pemphigoid

- Blisters
- Ulcers
- Desquamative gingivitis

Pemphigus

- Ulcers
- Blisters, rarely
- Desquamative gingivitis

Psoriasis

- White lesions
- Lesions like erythema migrans

Toxic epidermal necrolysis

- Ulcers

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SECTION 5

EPONYMOUS AND OTHER CONDITIONS

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43 Eponymous conditions

This chapter includes synopses of several eponymous conditions relevant to oral medicine, presented alphabetically.

Abrikossof's tumour. Granular cell myoblastoma (tumour).

Addison's disease(hypoadrenocorticism). Adrenocortical destruction, reduced cortisol, and subsequent increased release of pituitary adrenocorticotrophic hormone (ACTH). A rare disease of young or middle-aged females, the usual cause is autoimmune hypoadrenalism, rarely, tuberculosis, histoplasmosis (sometimes in HIV/AIDS) or carcinomatosis. Weight loss, weakness, and hypotension, with brown hyperpigmentation, especially in sites usually pigmented (areolae and genitals) or traumatized, in flexures, on the gingiva, and at the occlusal line are seen. Diagnosis is from low blood pressure, low plasma electrolyte and cortisol levels and impaired response to ACTH stimulation (Synacthen test). Management is fludrocortisone plus corticosteroids.

Adies' (Holmes-Adie) pupil. A benign condition. One pupil is dilated and reacts only very slowly to light or convergence together with loss of knee or ankle jerks.

Albers-Schonberg disease. Osteopetrosis.

Albright syndrome (McCune-Albright syndrome). Polyostotic fibrous dysplasia with skin pigmentation and an endocrine abnormality (usually precocious puberty in girls).

Alstrom syndrome. Congenital nerve deafness and retinitis pigmentosa.

Apert syndrome. Autosomal dominant craniofacial synostosis, which includes facial dysmorphology, limb (hands and feet) defects, and learning disability.

Argyll-Robinson pupils. Small, irregular, unequal pupils which fail to react to light, but do react to accommodation. Characteristically caused by neurosyphilis, may also be seen in diabetes, multiple sclerosis or other conditions.

Arnold-Chiari syndrome. A congenital malformation in which the brainstem and cerebellum are longer than normal and protrude into the spinal canal.

Ascher syndrome. Congenital double lip with blepharoclasis and thyroid goitre.

Avellis syndrome. A unilateral paralysis of the larynx and palate.

Bannayan-Riley-Ruvalcaba syndrome. A rare autosomal dominant disorder related to Cowden syndrome, affecting chromosome 10q and the PTEN (phosphatase and tensin homologue) gene, characterized by excessive growth before and after birth. The head is large (macrocephaly) and often long and narrow (scaphocephaly); normal intelligence or mild learning disability; pigmented macules on penis, tongue polyps and/or subcutaneous hamartomas.

Battle's sign. Bruising over the mastoid bone – sign of a basilar skull fracture.

Becker syndrome. Severe muscular dystrophy that results in progressive weakness of limb and breathing muscles.

Beckwith-Wiedemann syndrome. Congenital gigantism, and omphalocele or umbilical hernia.

Beeson's signs. Myalgia, facial oedema and fever in trichinosis.

Behçet syndrome. 'Adamantiades syndrome' (see Ch. 19).

Bell's palsy. The common lower motor neurone facial palsy (see Ch. 20).

Bell's sign. Seen in lower motor neurone facial palsy, when the eye rolls upward on attempted closure.

Bence-Jones protein. Immunoglobulin light chains which spill over into the urine (Bence-Jones proteinuria) when there is overproduction of γ -globulins in myelomatosis.

Biemond syndrome. Congenital obesity and hypogonadism.

Binder syndrome. Congenital maxillonasal dysplasia, and absent or hypoplastic frontal sinuses.

Blackfan-Diamond syndrome. Congenital red cell aplasia.

Block-Sulzberger disease (incontinentia pigmenti). Congenital hyperpigmented skin lesions, skeletal defects, learning disability and hypodontia.

Bloom syndrome. Congenital telangiectasia, depigmentation and short stature.

Bohn nodules. Keratin-filled cysts derived from palatal salivary gland structures scattered all over the palate, especially at the junction of the hard and soft palate.

Book syndrome. Autosomal dominant condition of palm and sole hyperhidrosis, hypodontia and premature whitening of hair.

Bourneville's disease (epiloia, tuberous sclerosis). Autosomal dominant; two loci – one on 9q34 and one

- on 16p13. A phakomatosis, there are fibromas at the nail bases (subungual fibromas); hamartomas in brain, kidneys and heart; and nodules in the nasolabial fold (adenoma sebaceum), plus pitting enamel hypoplasia.
- Bruton syndrome.** Sex-linked hypopimmunoglobulinaemia, cervical lymph node enlargement, oral ulceration, recurrent sinusitis, absent tonsils.
- Burkitt's lymphoma.** Caused by Epstein-Barr virus, most common in children in sub-Saharan African endemic malaria areas, especially Uganda and Kenya, characterized by lymphomatous deposits in many tissues, especially the jaws (in 50% of patients). Responds well to chemotherapy.
- Byar-Jurkiewicz syndrome.** Gingival fibromatosis, hypertrichosis, giant fibroadenomas of the breast, and kyphosis.
- Cannon's disease.** Congenital white sponge naevus.
- Carabelli's cusp.** Congenital additional palatal cusp on upper molars.
- Carney syndrome.** Autosomal dominant syndrome of myxomas, spotty lip pigmentation and endocrine overactivity. Cardiac myxomas cause death or serious disability in a quarter of affected patients.
- Castleman's disease.** A rare disorder characterized by benign tumours in lymph node tissue throughout the body [i.e. systemic disease (plasma cell type)].
- Chediak-Higashi syndrome.** A congenital immune defect in which neutrophils have large inclusions. Juvenile periodontitis and early tooth loss, plus oral ulceration.
- Christmas disease.** Blood clotting factor IX defect.
- Chvostek's sign.** Tapping the skin over the facial nerve elicits involuntary twitching of the muscles of the upper lip or ipsilateral side of face – a sign of hypocalcaemia.
- Cockayne syndrome.** Premature ageing, dwarfism, deafness and neuropathy.
- Coffin-Lawry syndrome.** Congenital osteocartilaginous anomalies and learning disability.
- Coffin-Siris syndrome.** Congenital defective neutrophil function, susceptibility to infection and skin pigmentation.
- Cohen syndrome.** Autosomal recessive syndrome of alveolar bone loss, neutropenia, learning disability and obesity.
- Costen syndrome.** Outmoded term relating to facial pain, otalgia and occlusal abnormalities, replaced by 'temporomandibular pain-dysfunction syndrome'.
- Cowden syndrome.** Autosomal dominant disorder affecting PTEN (phosphatase and tensin homologue) gene, congenital multiple hamartomas with oral papillomatosis and risk of breast and thyroid cancer.
- Coxsackie virus.** Named after a town in New York state, Coxsackie viruses are many, and can cause herpangina, hand, foot and mouth disease, and other illnesses.
- CREST syndrome.** Calcinosis, Raynaud's disease, oesophageal involvement, sclerodactyly and telangiectasia (see scleroderma, p. 368).
- Crohn's disease.** (see orofacial granulomatosis: OFG, p. 363). A chronic inflammatory idiopathic granulomatous disorder that may be caused by *Mycobacterium avium* subspecies *paratuberculosis*. Mutations in the CARD15 gene (NOD2 gene) are also implicated. About 20% have a blood relative with some form of inflammatory bowel disease. Cytokines, including tumour necrosis factor (TNF- α), interleukin-2, and interferon- γ are implicated. Crohn's disease can affect any part of the gastrointestinal tract, but mainly the ileum. About 10% of patients with bowel disease have oral lesions such as reddish raised gingival lesions, and hyperplastic mucosal folds, ulcers, facial swelling or angular cheilitis. Oral biopsy, haematological, gastrointestinal and other investigations may be required, also to exclude sarcoidosis and OFG. Histologically, the epithelium is intact, but thickened, with epithelioid cells and giant cells and a lymphocytic infiltration. Topical or intralesional corticosteroids may effectively control the lesions, but more usually systemic corticosteroids or salazopyrine are required. Immunomodulators, such as azathioprine and methotrexate, and newer biological medications, such as infliximab, may help.
- Cronkhite-Canada syndrome.** Hypogeusia followed by diarrhoea, and ectodermal changes including alopecia, nail dystrophy and skin and buccal melanotic hyperpigmentation. Colonic polyps may be present.
- Cross syndrome.** Athetosis, learning disability, gingival fibromatosis and hypopigmentation.
- Crouzon syndrome.** Autosomal-dominant premature fusion of cranial sutures, midface hypoplasia and proptosis.
- Curry-Jones syndrome.** Unilateral coronal synostosis and microphthalmia, plagiocephaly, craniofacial asymmetry, iris coloboma, broad thumbs, hand syndactyly, foot polydactyly, skin lesions, gastrointestinal abnormalities and developmental delay.
- Cushing syndrome.** Moon face with buffalo hump, hirsutism and hypertension due to an ACTH-producing pituitary adenoma.
- Darier's disease (Darier-White disease).** An autosomal-dominant skin disorder with follicular hyperkeratosis, and sometime white oral papules.
- Destombes-Rosai-Dorfman syndrome.** Rosai-Dorfman syndrome.
- Di George syndrome.** A third branchial arch defect related to a chromosome 22 anomaly (CATCH22 syndrome) causing immunodeficiency; cardiac, thyroid and parathyroid defects.
- Down syndrome (trisomy 21).** The commonest recognizable congenital chromosomal anomaly. Patients

are of short stature with characteristic brachycephaly, midface retrusion and upward sloping palpebral fissures (Mongoloid slant). Learning disability and dental anomalies and periodontitis are common.

Duhring's disease. Dermatitis herpetiformis.

Eagle syndrome. An elongated styloid process associated with dysphagia and pain on chewing, and on turning the head towards the affected side.

ECHO viruses. Enteric cytopathogenic human orphan viruses.

Ehlers-Danlos syndrome. A group of congenital collagen disorders (autosomal dominant, autosomal recessive, or X-linked), with altered mechanical properties of skin, joints, ligaments and blood vessels. Phenotypes vary depending upon which collagen type is affected. EDS is characterized by hyperflexible joints, hyperextensible skin, bleeding and bruising, and mitral incompetence. Patients can bend the thumb right back and may be able to touch the tip of their nose with their tongue. Recurrent dislocation of the temporomandibular joint may be seen. Dental anomalies include deep fissured premolars and molars, dentinal abnormalities, such as shortened deformed roots, and multiple large pulp stones. Ten types were described: in types IV, VIII and IX there is severe early onset periodontal disease with loss of permanent teeth. Type III genotypes show resistance to local analgesia.

Ellis-van Creveld syndrome. Also known as 'chondroectodermal dysplasia'. This syndrome mapped to chromosome 4p consists of congenital polydactyly, dwarfism, ectodermal dysplasia, hypodontia and hypoplastic teeth and multiple fraenae.

Epstein-Barr virus. A herpesvirus implicated in infectious mononucleosis, hairy leukoplakia, nasopharyngeal carcinoma and some lymphomas.

Epstein's pearls. Cystic keratin-filled nodules derived from entrapped epithelial remnants along the line of fusion along the midpalatine raphe.

Ewing's tumour. A primary malignant neoplasm of undifferentiated bone mesenchymal cells, extremely aggressive, expands rapidly, invades the soft tissues, and metastasizes early. Characteristically affects children and young adults, particularly males, but is rare in the jaws. Radiographically it has either a sunray or an onion-peel appearance due to deposition of new bone in layers. Microscopy shows sheets of uniform small round cells, with scanty, indistinct cytoplasm which contain glycogen. Treatment is chemo-radiotherapy, with a 5-year survival rate of over 50%.

Fabry's disease (angiokeratoma corporis diffusum universale). An X-linked recessive error of glycosphingolipid metabolism with angiokeratomas on scrotum, hypertension, fever, renal disease and risk of myocardial infarction.

Falot's tetralogy. The combination of a ventricular septal defect (VSD) with pulmonary stenosis, the aorta 'overriding' the VSD and right ventricular hypertrophy.

Fanconi's anaemia. Congenital anaemia, abnormal radii and risk of oral carcinoma and leukaemia.

Felty syndrome. Rheumatoid arthritis and neutropenia.

Fitzgerald-Gardner syndrome. Gardner syndrome.

Fordyce disease (Fordyce spots). See Chapter 28.

Frey syndrome. Gustatory sweating and flushing after trauma to skin overlying a salivary gland due to crossover of sympathetic and parasympathetic innervation to the gland and skin.

Froehlich syndrome. Congenital obesity, hypogonadism, and risk of learning disability and open bite.

Gardner syndrome. Familial adenomatous polyposis (FAP), formerly termed familial polyposis coli (FPC). An autosomal dominant condition caused by mutation in *APC* tumour suppressor gene on chromosome 5. Intestinal polyps have a 100% risk of undergoing malignant transformation, so early identification of disease is critical. Gardner described the occurrence of FAP with extracolonic manifestations of desmoids, osteomas and epidermoid cysts. Unerrupted and supernumerary teeth may be present. Multifocal pigmented lesions of the fundus of the eye are seen in 80%.

Garré's osteomyelitis. This is proliferative periostitis.

Gasserian ganglion. The trigeminal ganglion.

Gaucher disease. The most common genetic disease affecting Ashkenazi Jewish people of Eastern European ancestry, leading to a specific deficiency of the enzyme glucocerebrosidase and lipid-storage disorder. It may cause dry mouth.

Gilles de la Tourette syndrome. Coprolalia (utterance of obscenities).

Goldenhar syndrome. A variant of congenital hemifacial microsomia, presenting with microtia (small ears), agenesis of the mandibular ramus and condyle, vertebral abnormalities and epibulbar dermoids.

Goltz syndrome (focal dermal hypoplasia). An X-linked disorder with multiple mesenchymal defects, skin lesions, and oral warts and dental defects.

Gorlin-Goltz syndrome [Gorlin syndrome; multiple basal cell naevi syndrome; naevoid basal cell carcinoma syndrome (NBCCS)]. An autosomal-dominant trait related to chromosome 9q22.3-q31 and associated with *patch* gene mutations and deletions. The syndrome consists of multiple basal cell carcinomas (BCC), keratocystic odontogenic tumours (KCOTs), vertebral and rib anomalies and temporoparietal bossing with broad nasal root, calcification of the falx cerebri and abnormal sella turcica. Jaw cysts are indistinguishable from other KCOTs and are treated similarly. Diagnosis is suggested by major

criteria – positive family history; more than one BCC; KCOTs (first sign in 75%); palmar or plantar pits; or calcified falx cerebri. Minor criteria include congenital skeletal anomalies: bifid, fused, splayed or missing ribs; or bifid, wedged or fused vertebrae; occipitofrontal circumference over 97th percentile, with frontal bossing; cardiac or ovarian fibromas; medulloblastoma; lymphomesenteric cysts; and congenital malformations, such as cleft lip and/or palate, polydactyly, congenital ocular anomaly (cataract, microphthalmos, coloboma).

Graves disease. Hyperthyroidism with ophthalmopathy and exophthalmos.

Grinspan syndrome. Lichen planus, diabetes and hypertension (probably actually due to lichenoid reactions to antihypertensive and antidiabetic drugs).

Guillain-Barré syndrome. Acute infective polyneuritis; facial palsy may be seen.

Haemochromatosis. One of the most common metabolic errors, affecting only males, in which iron is excessively absorbed and deposits in tissues, causing hyperpigmentation, diabetes, hypogonadism, cirrhosis and cardiomyopathy.

Hailey-Hailey disease. Autosomal-dominant, benign familial pemphigus presenting in the second or third decade with skin and oral blisters and vegetations.

Haim-Munk syndrome. Similar to Papillon-Lefevre syndrome, plus pyogenic skin infections, arachnodactyly, acro-osteolysis, onychogryphosis and pes planus.

Hajdu-Cheney syndrome. Rare connective tissue disorder, featuring ulcerating lesions on the palms and soles, accompanied by softening and destruction of bones (acro-osteolysis). Abnormal development of bones, joints and teeth also occurs.

Hallerman-Streiff syndrome. Congenital cranial anomalies, micro-ophthalmia, cataracts, mandibular hypoplasia and abnormal temporomandibular joint.

Hand-Schüller-Christian disease. Langerhans histiocytosis.

Hansen's disease. Leprosy.

Heck's disease (focal epithelial hyperplasia).

Papillomas caused by human papilloma viruses 13 or 32, seen especially in ethnic groups such as American Indians and Inuits.

Heefordt syndrome. Sarcoidosis associated with lacrimal and salivary swelling, uveitis and fever (uveoparotid fever) and facial palsy.

Henoch-Schönlein purpura. Allergic purpura, which may cause oral petechiae.

Hermansky-Pudlak syndrome. Congenital albinism and bleeding tendency.

Hodgkin's disease. Lymphoma that affects particularly males in middle age. Progressive lymphoid tissue involvement, often begins in the neck with enlarged, discrete and rubbery lymph nodes. Drinking alcohol may cause pain in affected lymph nodes. Pain, fever,

night sweats, weight loss, malaise, bone pain and pruritus are common. Treatment by chemotherapy and radiotherapy is remarkably successful.

Horner syndrome. This is caused by interruption of sympathetic nerve fibres peripherally as a result, for example, of trauma to the neck, or lung cancer infiltrating the superior cervical sympathetic ganglion, and comprises, usually, unilateral:

- miosis (pupil constriction)
- ptosis (drooping of the upper eyelid)
- loss of sweating of the ipsilateral face
- apparent enophthalmos (retruded eyeball).

Horton's cephalgia. Migrainous neuralgia.

Hunterian chancre. Syphilitic primary chancre.

Hurler syndrome. Congenital mucopolysaccharidosis causing growth failure, learning disability, large head, frontal bossing, hypertelorism, coarse facial features (gargoylism) and mandibular radiolucencies.

Hutchinson-Gilford syndrome. Progeria (see Werner syndrome, p. 366).

Hutchinson's teeth. Screwdriver-shaped incisor teeth in congenital syphilis.

Hutchinson's triad. Hutchinson's teeth, interstitial keratitis and deafness.

Jackson-Lawler syndrome. A type of pachyonychia congenita with no oral leukoplakia, but neonatal teeth and early loss of secondary teeth.

Jadarsohn-Lewandowski syndrome. Pachyonychia congenita.

Jones syndrome. Curry-Jones syndrome.

Kaposi sarcoma (KS). A malignant neoplasm of endothelial cells caused by human herpesvirus 8, seen especially in HIV/AIDS or immunosuppressed patients. Usually oral lesions are part of more widespread disease. KS early lesions are red, purple or brown macules, later becoming nodular, extending, ulcerating and disseminating. KS typically involves the palate or gingivae. Diagnosis is confirmed by biopsy. Epithelioid angiomatosis, haemangiomas, lymphomas and purpura may need to be differentiated. Management is treatment of the underlying predisposing condition if possible; and then radiotherapy or vinca alkaloids systemically or intralesionally.

Kartagener's syndrome (primary ciliary dyskinesia, PCD) Congenital dextrocardia, immunodeficiency, sinusitis and recurrent respiratory infections (and male infertility).

Kawasaki disease (mucocutaneous lymph node syndrome). Fever, cheilitis, lymphadenopathy, desquamation of hands and feet, and cardiac lesions in periodic epidemics with geographic spread, suggest an infectious aetiology. Management includes gamma globulin and aspirin and long-term anticoagulation.

Kikuchi-Fujimoto disease. A self-limiting idiopathic illness of pyrexia, neutropenia and cervical lymphadenopathy in young Asian women. Can be confused histologically and clinically with lymphoma or systemic lupus erythematosus.

Kimura's disease. A chronic idiopathic inflammatory condition presenting with a painless, slowly enlarging soft tissue mass (or masses), associated lymphadenopathy and peripheral eosinophilia; 85% of cases are seen in males.

Klinefelter syndrome. A chromosome abnormality in men, causing hypogonadism.

Klippel-Feil anomaly. Congenital association of cervical vertebrae fusion and short neck, low-lying posterior hairline, syringomyelia and other neurological anomalies, and sometimes unilateral renal agenesis and cardiac anomalies.

Koplik's spots. Small white spots on the buccal mucosa during measles prodrome.

Kveim test. An outdated skin test for sarcoidosis.

Laband syndrome (Zimmerman-Laband syndrome). A form of hereditary gingival fibromatosis with skeletal anomalies and large digits.

Langerhans cell histiocytoses (histiocytosis X). Rare neoplasms arising from Langerhans cells (dendritic intraepithelial macrophage-like cells). Swelling and gingival ulceration, particularly in molar region, are common and teeth may loosen and exfoliate. Failure of healing of a socket, or the appearance of a pathological fracture may be presenting features. The spectrum includes the following:

- Solitary eosinophilic granuloma of bone: usually benign with osteolytic lesion only and seen in adults. There is sometimes gross periodontal destruction.
- Multifocal eosinophilic granuloma (Hand-Schuller-Christian disease): a more malignant form in children and young adults characterized by osteolytic lesions and sometimes diabetes insipidus and proptosis.
- Letterer-Siwe disease: the most malignant form; seen in infants and characterized by failure to thrive, fever, hepatosplenomegaly and skeletal osteolytic lesions that may cause pain, swelling and loosening of teeth.

Differentiate from other osteolytic disorders, especially carcinomatosis and myelomatosis. Diagnose by radiography and biopsy: foamy macrophages (Birbeck granules may be seen by EM), eosinophils and bone destruction. Surgery used to manage solitary lesions; radiotherapy/chemotherapy for multifocal disease.

Larsen syndrome. A mainly autosomal recessive condition, consisting of cleft palate, flattened facies,

multiple congenital dislocations and deformities of the feet.

Laurence-Moon-Biedl syndrome. Congenital retinitis pigmentosa, obesity, polydactyly, learning disability and blindness.

Laugier-Hunziker syndrome (Laugier-Hunziker-Baran syndrome). Labial and oral mucosal brown to black pigmented macules and nail hyperpigmentation.

Leopard syndrome (cardiocutaneous lentiginosis syndrome). LEOPARD syndrome and Noonan syndrome are allelic disorders caused by different mutations in *PTPN11*, a gene encoding the protein tyrosine phosphatase SHP-2 located at chromosome 12q24.1. It consists of:

- lentigines (multiple)
- electrocardiographic conduction abnormalities
- ocular hypertelorism
- pulmonary stenosis
- abnormalities of genitalia
- retardation of growth
- deafness.

Lesch-Nyhan syndrome. Congenital defect of purine metabolism causing learning disability, choreoathetoid cerebral palsy and aggressive self-mutilation.

Letterer-Siwe disease. Langerhans histiocytosis.

Lewar's disease (pulse granuloma). A hard mass in the lower buccal sulcus indented or ulcerated by a denture flange. Hyaline bodies seen subperiosteally on histology are vegetable leguminous pulses, which provoke a foreign body reaction. Vegetable matter becomes embedded under the mucosa following tooth extraction or from denture pressure. Treatment is by curettage.

Lowe syndrome (cerebrohepatorenal syndrome). Congenital hypotonia and flexion contractures.

Ludwig's angina. Infection of sublingual and submandibular fascial spaces.

Lyell's disease (toxic epidermal necrolysis). (Originally described in relation to staphylococcal infection.)

Lyme disease. Infection with *Borrelia burgdorferi* from deer ticks, causing rashes, fever, arthropathy and facial palsy. First recognized in the town of Lyme, Connecticut, USA, but prevalent worldwide.

Maffucci syndrome. Multiple enchondromas, haemangiomas (often in the tongue), and risk of malignant chondrosarcomas.

MAGIC syndrome. Mouth And Genital ulcers and Intertitial Chondritis. A variant of Behçet syndrome.

Mantoux test. Skin test for delayed-type hypersensitivity reaction to bacillus Calmette Guérin (BCG; for tuberculosis).

Marcus Gunn syndrome. Jaw-winking syndrome (eyelid winks during chewing), with ptosis.

Marfan syndrome. An autosomal-dominant condition linked to chromosome 15 in FBN1 gene, which codes for fibrillin-1, essential for the formation of elastic fibres. Reduced levels of fibrillin-1 allow transforming growth factor (TGF β) to damage heart and lungs. Prevalent among basketball and volleyball players, patients are tall, thin and with arachnodactyly (long, thin spider-like hands). There may be spontaneous pneumothorax, lens dislocation, aortic regurgitation or dissecting aneurysms, mitral valve prolapse, and palate is occasionally cleft or with bifid uvula. Joint laxity is common and TMJ may dislocate. Multiple dental cysts are less common oral complications.

Can be confused with Loeys-Dietz syndrome, caused by mutations in the TGF β receptor genes TGF β R1 and TGF β R2.

Marie-Sainton syndrome. Cleidocranial dysplasia.

Melkersson-Rosenthal syndrome. The rare association of facial swelling (usually granulomatous cheilitis), with facial palsy and fissured tongue.

Miescher's cheilitis. Oligosymptomatic labial granulomatosis or Crohn's disease.

Mikulicz disease. Salivary gland and lacrimal gland swelling, often related to Sjögren syndrome.

Mikulicz syndrome. Salivary gland and lacrimal gland swelling related to malignant disease.

Mikulicz ulcer. Minor aphthous ulceration.

Moebius syndrome. A complex congenital anomaly involving multiple cranial nerves, affecting mainly the abducens and facial nerves, and often associated with limb anomalies. Muscle transplantation has been used to address the lack of facial animation, lack of lower lip support and speech difficulties.

Moon's molars. Hypoplastic molars from congenital syphilis.

Munchausen syndrome. The fabrication of stories by the patient, aimed at the patient receiving operative intervention.

Murray syndrome. Multiple hyaline dermal tumours, gingival fibromatosis and recurrent infections.

Murray-Puretic-Drescher syndrome (juvenile hyaline fibromatosis). A rare autosomal recessive disease characterized by cutaneous nodules, especially around the head and neck and often involving the lips. The effects increase with age and also include joint contractures, gingival swelling and osteolytic lesions.

Nelson syndrome. A rare condition with hyperpigmentation caused by ACTH overproduction in response to adrenalectomy, used for breast cancer.

Neumann's bipolar aphthosis. The association of recurrent aphthae with genital ulceration; probably this is a stage in the development of Behçet syndrome.

Nikolsky sign. A term meaning blistering, or the extension of a blister, on gentle pressure (seen mainly in pemphigus and pemphigoid).

Non-Hodgkin's lymphomas (NHL). More common than Hodgkin's disease and generally with a poorer prognosis, and a predilection for the gastrointestinal tract and central nervous system. Enlargement of cervical lymph nodes is often the first sign, but NHL may occur in the gingivae or faucial region; a recognized complication of HIV/AIDS and may be Epstein-Barr virus related.

Noonan syndrome (see also Leopard syndrome, page 341). Congenital short stature and webbed neck, sometimes with cardiac anomalies, pulmonary stenosis and cherubism.

Ollier syndrome. Multiple enchondromas.

Osler-Rendu-Weber disease (hereditary haemorrhagic telangiectasia; HHT). An autosomal-dominant disorder where telangiectases are present orally, periorally and in the nose, gastrointestinal tract and occasionally on the palms. Telangiectases may bleed, and cryosurgery or laser treatment may be needed.

Paget's disease of bone. A bone disorder in elderly males which may affect up to 5% of those over 55 years of age. The aetiology is unclear and incidence appears to be decreasing. Viruses, particularly paramyxoviruses such as canine distemper or measles virus, have been implicated – but with little evidence. There is a strong genetic component; 15–20% have a first-degree relative with Paget disease. Mutations in *sequestosome 1/p62* gene (SQSTM1/p62) are seen in about one-third, and in 5–15% of patients with no family history. SQSTM1/p62 protein is a selective activator of the transcription factor NF κ B, which plays an important role in osteoclast differentiation and activation in response to the cytokines RANK-ligand and interleukin-1.

Paget's disease is characterized by the total disorganization of the normally orderly remodelling of bone and an anarchic alternation of bone resorption and apposition – 'reversal lines' (Fig. 43.1) often with severe bone pain. In early lesions, bone destruction predominates (osteolytic stage) and there is bowing of long bones, especially the tibia, pathological fractures, broadening/flattening of chest and spinal deformity. If Paget's disease is widespread, the increased bone vascularity can lead to high output cardiac failure. As disease activity declines, bone apposition increases (osteosclerotic stage) and bones enlarge. If the skull is affected, the patient may notice hat becomes tight. Constriction of skull foraminae may cause cranial neuropathies. The maxilla often enlarges, particularly in the molar region, with widening of the alveolar ridge and any dentures may appear to become too tight. The dense bone, hypercementosis and loss of lamina dura make extractions difficult, and there is a liability to haemorrhage and infection. Diagnosis is supported by imaging, biochemistry and histopathology. In early

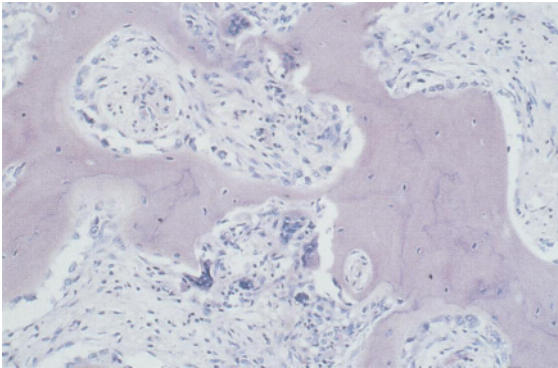


Fig 43.1 Paget's disease showing bone reversal lines from resorption/deposition with a 'mosiac pattern'.

lesions, large irregular areas of relative radiolucency (osteoporosis circumscripta) are seen, but later there is increased radio-opacity, with appearance of an irregular 'cotton wool' pattern. There is progressive thickening of the diploe and base of the skull as well as the sphenoid, orbital and frontal bones. Isotope bone scanning shows localized areas of very high uptake. Increase in plasma alkaline phosphatase and urine hydroxyproline levels, but little or no changes in serum calcium or phosphate levels. Differential diagnosis includes other fibro-osseous lesions, such as fibrous dysplasia, and conditions with a raised alkaline phosphatase, such as osteomalacia, hyperparathyroidism and osteoblastic metastatic deposits (e.g. prostate carcinoma). Bisphosphonates are the treatment.

Papillon-Lefevre syndrome. A congenital condition mapped to chromosome 11q with a defect in the polymorphonuclear leukocyte lysosomal enzyme cathepsin c, causing palmoplantar hyperkeratosis and juvenile periodontitis, which affects both dentitions, and immunodeficiency. Acitretin may correct the defective CD3-induced T lymphocyte activation.

Parrot's nodes. Frontal bossing in congenital syphilis.

Patterson-Kelly-Brown syndrome (Plummer-Vinson syndrome). The association of dysphagia (due to a post-cricoid web of *Candida* which is premalignant), microcytic hypochromic anaemia, koilonychia (spoon-shaped nails) and angular cheilitis (secondary to the anaemia).

Paul-Bunell test (Paul-Bunell-Davidson or Forssman Antibody Test). A serological test for heterophile antibodies in infectious mononucleosis (glandular fever).

Peutz-Jeghers syndrome. An autosomal-dominant condition due to a chromosome 19p *STK11/LKB1* (serine/threonine kinase 11) gene mutation. It consists of circumoral melanosis and intestinal polyposis. Oral brown or black macules appear in infancy and affect especially the lips and buccal mucosa and may be seen on extremities and abdomen. The intestinal polyposis may cause intussusception or other types of obstruction. Almost 50% of patients develop and

die from some type of cancer by age 57 years – often extra-intestinal cancers.

Pierre-Robin syndrome. Congenital micrognathia, cleft palate and glossoptosis.

Pindborg tumour. Calcifying epithelial odontogenic tumour.

Plummer-Vinson syndrome. Patterson-Kelly-Brown syndrome.

Popischill-Feyrter aphthae. A term used for palatal ulceration in neonates.

Prader-Willi syndrome. Congenital obesity, hypogonadism, learning disability, diabetes and dental defects.

Ramon syndrome. Cherubism, arthritis, epilepsy, gingival fibromatosis, hypertrichosis and learning disability.

Ramsay-Hunt syndrome. A lower motor neurone facial palsy due to herpes zoster of the geniculate ganglion of the seventh nerve. Presents with vesicles in the ipsilateral pharynx, external auditory canal and on the face.

Rapp-Hodgkin syndrome. Ectodermal dysplasia, kinky hair, cleft lip/palate, popliteal pterygium and ectrodactyly.

Raynaud syndrome. A vascular spasm in response to cooling, seen in the digits in connective tissue disorders.

Reiter's disease. The association of arthritis, urethritis and balanitis, and conjunctivitis, found mainly in men with HLA-B27 and a high incidence of sexually transmitted infections (mainly Chlamydia). Reiter's disease is the most common cause of arthritis in young men. A postdysenteric form is more common in women, often after infection with *Shigella flexneri*, *Salmonella typhimurium*, *Yersinia enterocolitica*, *Campylobacter jejuni*, or *Chlamydia trachomatis*. Oral lesions are circinate papules on the palate and elsewhere. Skin lesions resemble psoriasis on the palms and soles (keratoderma blennorrhagica). Treatment is with non-steroidal anti-inflammatory drugs.

Rett syndrome. Congenital bruxism and hand-wringing, often with learning disability.

Rieger syndrome. Congenital ocular anomalies, iridal hypoplasia, glaucoma and blindness, maxillary hypoplasia and dental hypoplasia with oligo- and microdontia.

Riley-Day syndrome. Inherited familial dysautonomia; sympathetic dysfunction, salivary swelling, sialorrhoea and self-mutilation, seen particularly in Ashkenazi Jews.

Romberg syndrome (hemifacial atrophy). Progressive atrophy of the soft tissues usually of half the face, associated with contralateral Jacksonian epilepsy and trigeminal neuralgia. It starts in the first decade and lasts about 3 years before it becomes quiescent.

Rosai-Dorfmann syndrome (Sinus histiocytosis with massive lymphadenopathy or Destombes-Rosai-Dorfman syndrome.) A benign, non-Langerhans cell, histiocytic proliferative disorder that primarily affects lymph nodes.

Rothmund-Thomson syndrome. Congenital poikiloderma, hypogonadism, dwarfism, cataracts and microdontia.

Rubinstein-Taybi syndrome (broad thumb-great toe syndrome). Short stature with a small head size, and developmental delay. The most striking physical feature is broad, sometimes angulated thumbs and first toes. Facial features include a prominent beaked nose and down-slanting eyes. Undescended testes occur in males.

Rutherford syndrome. Corneal dystrophy, neurosensory hearing loss, gingival fibromatosis and delayed tooth eruption.

Ruvalcaba-Myrhe-Smith syndrome. Bannayan-Riley-Ruvalcaba syndrome (see p. 337).

Sabin-Feldmann test. Serological test for toxoplasmosis.

Saethre-Chotzen syndrome. An autosomal-dominant craniosynostosis associated with cleft palate as well as other disturbances of the facial skeleton and extremities.

Saxon test. A simple, reproducible, cheap test for xerostomia, which involves chewing on a weighed sterile sponge for 2 minutes and then re-weighing the sponge. Normal subjects produce at least 2.75g of saliva in 2 minutes.

Schmidt syndrome. Congenital hypoadrenocorticism, hypoparathyroidism, diabetes and malabsorption, with candidiasis.

Seckel syndrome. Congenital microcephaly, learning disability, zygomatic and mandibular hypoplasia.

Sipple syndrome. Multiple endocrine neoplasia (MEN) type 3 (MEN 3; sometimes called 2b) affecting several endocrine glands with multiple mucosal neuromas, pheochromocytoma and medullary thyroid carcinoma (calcitonin levels raised).

Sjögren-Larsson syndrome. Congenital ichthyosis, learning disability, cerebral palsy and indifference to pain.

Sjögren syndrome. See Chapter 37.

Sluder syndrome. Migrainous neuralgia.

Smith-Lemli-Opitz syndrome. Congenital short stature, learning disability, syndactyly, urogenital and maxillary anomalies.

Stafne bone cavity. An ectopic inclusion of salivary tissue in the mandible, often from the submandibular gland. Radiography shows a cystic radiolucency. No treatment is indicated, but if a diagnosis cannot be confirmed by sialography, or if serial radiographs show an increase in cavity size, exploratory surgery is indicated.

Stevens-Johnson syndrome. See Chapter 26.

Still syndrome. Juvenile rheumatoid arthritis.

Sturge-Weber syndrome (encephalotrigeminal angiomas). A congenital hamartomatous angioma of the upper face (naevus flammeus), oral mucosa and underlying bone (with hemihypertrophy of bone and accelerated eruption of associated teeth), extending intracranially to cause convulsions, and contralateral hemiplegia and intracerebral calcifications, and sometimes learning disability.

Sutton's ulcers. Major aphthae.

Sweet syndrome. Acute neutrophilic dermatosis with erythematous, well-demarcated skin papules and plaques; red mucosal lesions and ulcers, often associated with malignant disease or induced by drugs. Treatment is with systemic steroids.

Takayasu's disease. Pulseless aorta and large arteries.

Thibierge-Weissenbach syndrome. The CREST syndrome.

TORCH syndrome. Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes simplex induced fetal abnormalities

Treacher-Collins syndrome (mandibulofacial dysostosis). Autosomal-dominant first branchial arch defect with downward sloping (anti-mongoloid slant) palpebral fissures, hypoplastic malar complexes, mandibular retrognathia, deformed pinnae, hypoplastic sinuses, eye colobomas, and middle and inner ear hypoplasia (deafness).

Trotter syndrome. Acquired unilateral deafness, pain in the mandibular (third) division of the trigeminal nerve, ipsilateral palatal immobility, and trismus due to invasion of the nasopharynx and the trigeminal nerve by a malignant tumour. *Pterygopalatine fossa syndrome* is a similar condition, where the first and second divisions of the trigeminal nerve are affected.

Turner syndrome. Complete or partial deletion of the X chromosome. Affects females only, with short stature, low hairline, web neck, broad chest and widely spaced nipples, increased carrying angle of the elbows and non-functioning ovaries. Occasionally cherubism is found.

Turner's tooth. Hypoplastic tooth due to damage to the developing tooth germ.

Tzanck cells. Abnormal epithelial squames in pemphigus or herpetic infections.

Von Recklinghausen's disease. Multiple neurofibromas with skin pigmentation, skeletal abnormalities and central nervous system involvement.

Von Willebrand's disease. Common bleeding disorder caused by defective blood clotting factor VIII and platelet dysfunction.

Waardenburg syndrome. Congenital heterochromia iridis (different coloured eyes), deafness, and white forelock, with prognathism.

Waldeyer's ring. Lymphoid tissue surrounding the entrance to the oropharynx (tonsils and adenoids).

Warthin's tumour. Benign salivary gland neoplasm – adenolymphoma or papillary cystadenoma lymphomatosum.

Wegener's granulomatosis (Idiopathic disseminated malignant granulomatosis.) A rare, idiopathic disorder of necrotizing granulomatosis. Initially affecting the respiratory tract, arteritis affects small vessels in lungs, kidneys, eyes, skin, muscles, joints and mouth and is potentially lethal. A painless progressive swelling of the gingiva in a previously healthy mouth, particularly associated with swollen inflamed papillae with a fairly characteristic 'strawberry-like' appearance, should arouse suspicion. Diagnosis is supported by biopsy, imaging and anti-neutrophil cytoplasmic antigens (ANCA), anaemia, elevated erythrocyte sedimentation rate (ESR) and white blood cell and platelet counts. Management is antimicrobials, cytotoxic agents or radiotherapy.

Werner syndrome. Congenital alopecia, dwarfism, senility, early atherosclerosis, delayed tooth eruption and mandibular hypoplasia.

Whipple disease. A rare potentially lethal bacterial infection with *Tropheryma whippelii* that infects the small bowel to cause malabsorption, but may affect immune system, heart, lungs, brain, joints, and eyes.

William syndrome. Genetic disorder characterized by mild learning disability, unique personality characteristics, distinctive facial features and cardiovascular disease (elastin arteriopathy). A range of connective tissue abnormalities is observed and hypercalcaemia and/or hypercalciuria are common.

Wilson syndrome (hepatolenticular degeneration). Disorder of copper metabolism leading to hepatic disease; renal disease; spasticity; tremor and mental problems.

Wiskott–Aldrich syndrome. X-linked recessive immunodeficiency with thrombocytopenia, infections, eczema (TIE syndrome) and lymphoreticular malignancies.

Witkop's disease. Hereditary benign intraepithelial dyskeratosis – seen mainly in parts of the USA.

Zimmerman–Laband syndrome. Laband syndrome.

Further reading

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44 Other conditions

This chapter includes synopses of a number of conditions relevant to oral medicine, not appearing elsewhere, and presented alphabetically. If a specific condition is not found here, please refer to the index, since it may well be located elsewhere in the book.

Acanthosis nigricans. A rare paraneoplastic condition where papillomatous oral lesions are seen often in patients with internal malignancy.

Acatalasia. Autosomal recessive defect in the enzyme catalase, which normally removes reactive oxygen species, such as hydrogen peroxide, from tissues. Severe periodontal destruction and oral ulceration can result.

Achondroplasia (chondrodystrophia fetalis). An autosomal dominant condition in which endochondral ossification is reduced. The most common form of short-limbed dwarfism – patients have disproportionately short limbs, bowed legs, kyphosis, prominent buttocks and abdomen, and trident hands with short fingers. The skull is relatively large, having prominent frontal, occipital and parietal bones. The middle third of the face can be hypoplastic with nasal bridge depressed and a class III type malocclusion. The foramen magnum is often narrow and spinal cord compression can occur. Joints can be of limited mobility and the pelvic inlet narrow.

Acrodermatitis enteropathica. A rare genetic disorder of zinc metabolism causing mouth ulceration and candidiasis, rash around orifices, and alopecia.

Actinic cheilitis. A diffuse degenerative change, typically of the lower lip, from extreme sun (ultraviolet light) damage, often since youth (ski-ing/windsurfing/sailing, etc.). The lip becomes swollen and red in acute cheilitis, with white plaques (leukoplakias) and ulcers in chronic cheilitis. A potentially malignant lesion (6% risk of squamous carcinoma), biopsy is mandatory. Dysplastic lesions should be excised.

Actinomycosis. A rare infection with *Actinomyces israelii*, below the mandibular angle (not lymph nodes) that may follow jaw fracture or tooth extraction. Prolonged therapy, usually with penicillin, is indicated.

Acute necrotizing (ulcerative) gingivitis. A non-contagious anaerobic gingival infection associated with overwhelming proliferation of *Borrelia vincentii* and fusiform bacteria. Predisposing factors include smoking, viral respiratory infections and immune defects, such as in HIV/AIDS. Uncommon, except in lower socioeconomic classes, this typically affects

adolescents and young adults, especially in institutions, armed forces, etc., or people with HIV/AIDS.

Characteristic features include severe gingival soreness, profuse bleeding, halitosis and a bad taste. Interdental papillae are ulcerated with necrotic slough. Malaise, fever and/or cervical lymph node enlargement (unlike herpetic stomatitis) are rare. Cancrum oris (noma) is a very rare complication, usually in debilitated children.

Diagnosis is usually clinical. Smear for fusospirochaetal bacteria and leucocytes; blood picture occasionally. Differentiate from acute leukaemia or herpetic stomatitis. Manage by oral debridement, metronidazole (penicillin if pregnant) and oral hygiene.

Amalgam tattoo. A black or bluish-black asymptomatic usually solitary small pigmented area beneath normal mucosa; often close to the lower ridge or vestibule caused by amalgam particles or dust becoming incorporated in healing wounds after tooth extraction or apicectomy or beneath mucosa. Diagnosis is from clinical features, but it may rarely be radio-opaque. It may be necessary to excise to exclude melanoma.

Amelogenesis imperfecta. A rare genetic defect of enamel formation due to mutations in AMELX, ENAM, and MMP20 genes, with a wide variety of patterns. All teeth are equally affected, as are other family members. Diagnosis is from clinical features (Fig. 44.1, Table 44.1). Fluorosis, tetracycline staining, dentinogenesis imperfecta and oculodentodigital



Fig. 44.1 Amelogenesis imperfecta

Table 44.1
Amelogenesis imperfecta

Type	1	2	3	4
<i>Named</i>	Hypoplastic	Hypocalcified	Hypomaturation	Hypomaturation with taurodontism
<i>Defect</i>	Matrix	Calcification	Maturation	Mixed – between types 1 and 3
<i>Enamel thickness and colour</i>	Thin, hard, pitted or grooved	Normal thickness, softer and liable to attrition. Discoloured white to brownish-yellow, and darkening with age	Normal thickness, softer and liable to attrition.	
<i>Radiographic features</i>	Normal enamel density	Enamel similar to dentine		
<i>Inheritance</i>	AD, AR or x	AD or AR	AD, AR or x	AD

dysplasia may need to be differentiated. Management requires restorative dental care.

Amyloidosis. The deposition in tissues of amyloid – an eosinophilic hyaline material, with a fibrillar structure on ultramicroscopy. Amyloid can be identified via Congo red stain under fluorescent or polarized light, thioflavine T stain under fluorescent light, or immunoreactivity with antibodies for immunoglobulin light chains.

Primary (including myeloma-associated) amyloidosis – associated with deposits of immunoglobulin light chains. Manifestations include macroglossia and oral petechiae or blood-filled bullae (secondary purpura).

Secondary amyloidosis – seen mainly in rheumatoid arthritis and ulcerative colitis, rarely affects the mouth, and is associated with deposits of AA proteins.

Diagnose from biopsy; blood picture; raised erythrocyte sedimentation rate (ESR) and marrow biopsy; serum proteins and electrophoresis; urinalysis (Bence-Jones proteinuria); skeletal survey for myeloma. Manage by chemotherapy (melphalan, corticosteroids or flouxymesterone).

Aneurysmal bone cyst. Not a cyst, the aetiology remains obscure: approximately one-third appear to be associated with other bone disorders, such as a giant cell lesion, fibrous dysplasia and ossifying fibromas. This rare lesion presents as an asymptomatic hard swelling of the jaw, sometimes following a history of trauma. It may occur in any part of the skeleton. Radiographs show a unilocular, or multilocular translucency with a honeycomb or soap-bubble appearance. Preoperative aspiration shows bloody fluid with a low haematocrit, differentiating it from undiluted blood in a vascular anomaly, such as haemangioma. Diagnosis confirmed by histology, which shows numerous capillaries and blood-filled spaces, areas of haemorrhage associated with multinucleated giant cells and irregular areas of osteoid. Treat by thorough curettage or excision.

Angina bullosa haemorrhagica (localized oral purpura). Blood blisters in the mouth or pharynx, mainly on soft palate, seen in absence of any immunological or platelet-associated cause. Seen mainly in older people, the aetiology is unclear, though there are occasional associations with use of steroid inhalers. There is rapid onset, with breakdown of the blister in a day or two to an ulcer. Diagnose from clinical features, although it may be necessary to confirm haemostasis is normal; and rarely to biopsy to exclude pemphigoid. Manage by reassurance. Topical analgesics may provide symptomatic relief.

Angiomas. See haemangiomas (p. 357).

Angiomyoma. A rare benign hamartoma involving blood vessels and muscle.

Ankyloglossia (tongue-tie). An uncommon genetic condition which results in the lingual fraenum anchoring the tongue tip, restricting tongue protrusion and lateral movements. Oral cleansing (but not speech) is impaired. Differentiate from tethering by scarring. Management is surgery (fraenectomy) if severe.

Antral carcinoma. A rare, usually squamous carcinoma, seen mainly in elderly males – the only identified predisposing factor being occupational exposure to wood dust. Initially asymptomatic, it may cause swelling or pain when the carcinoma invades. Symptoms depend on the main direction of spread:

- Oral invasion; causes pain and swelling of palate, alveolus or sulcus; teeth may loosen.
- Ocular invasion; causes pain and swelling, ipsilateral epiphora, diplopia or proptosis.
- Nasal invasion; causes nasal pain and swelling, obstruction or a blood-stained discharge.

Diagnose from radiographs, magnetic resonance imaging (opaque antrum and later destruction of antral wall or floor), and biopsy. Manage by surgery (sometimes with radiotherapy). Prognosis is 10–30% 5-year survival.

Black hairy tongue. Black hairy tongue affects mainly the posterior tongue; the filiform papillae are excessively long and stained black or brown. It appears to be caused by the accumulation of epithelial squames and proliferation of chromogenic micro-organisms. It is more common:

- in smokers
- in people with hyposalivation
- where the diet is soft
- where antimicrobials are used
- where oral hygiene is wanting.

Patients with black hairy tongue may find the condition improved by:

- increasing their oral hygiene
- using a tongue scraper
- brushing the tongue before retiring at night, with a hard toothbrush and cold water
- using sodium bicarbonate mouthwashes
- eating pineapple or sucking a peach stone
- chewing gum.

Occasionally, it may be caused by antimicrobial therapy, especially with broad-spectrum drugs, such as tetracyclines. Superficial transient brown discolouration of the dorsum of the tongue and sometimes other soft tissues may be caused by cigarette smoking, tobacco or betel chewing, some drugs (such as iron salts), some foods and beverages (such as coffee and tea), liquorice and chlorhexidine. Such discolouration is easily brushed off.

Branchial cyst. A lymphoepithelial cyst that may arise from enclavement of salivary tissue in a lymph node, or from the cervical sinus. It usually becomes apparent in the third decade. It requires excision.

Bullous pemphigoid. An autoimmune disease usually with widespread crops of tense, fluid-filled blisters on the skin. The diagnosis is confirmed by biopsy. Bullous pemphigoid is treated with prednisolone.

Caries. Dental caries can occur on any tooth surface exposed to the oral environment, but not surfaces retained within bone. There are four factors in the aetiology: a tooth surface (enamel or dentine); cariogenic (or potentially caries-causing) bacteria in dental plaque; fermentable carbohydrates; and time. The specific bacterial species believed to cause caries include *Streptococcus mutans* and *Lactobacilli*. Particularly for root caries, the most closely associated bacteria are *Lactobacillus acidophilus*, *Actinomyces viscosus*, *Nocardia* spp., and *Strep. mutans*. Sugars (sucrose, glucose, fructose) are metabolized to acetic, lactic, formic and succinic acids. Different individuals are susceptible to different degrees depending on tooth shape, oral hygiene, and the flow and buffering capacity of their saliva.

Carotid body tumour. A slow-growing, but malignant neoplasm of chromaffin cells that both invades locally and metastasizes. It presents as a mass over the internal carotid artery and transmits the carotid pulsation. It must be resected.

CATCH22. Stands for cardiac abnormality, abnormal facies, T-cell deficit due to thymic hypoplasia, cleft palate, and hypocalcaemia due to hypoparathyroidism, caused by a chromosome 22 defect.

Cheek biting (morsicatio buccarum). Common and seen in adults mainly, especially anxious patients, and those with other psychologically related disorders, e.g. temporomandibular pain-dysfunction syndrome, it is also rarely caused by self-mutilation, seen in psychiatric disorders, learning disability, Lesch-Nyham syndrome (p. 341) and some rare syndromes with insensitivity to pain. Abrasion of the superficial epithelium leaves whitish fragments on reddish background. The lesions are invariably restricted to the lower labial mucosa and/or buccal mucosa near the occlusal line on one or both sides.

Chemical burns. Can be caused by various chemicals or drugs; notably aspirin put in the sulcus to try to relieve toothache, or cocaine. A white lesion with sloughing mucosa is seen. Diagnosis is by history and clinical features.

Cherubism. A genetically determined jaw disease which closely resembles fibrous dysplasia except for the autosomal dominant inheritance (but variable expression) and association with chromosome 4p and mutated gene SH3BP2 which codes for a c-Abl-binding protein. It presents at 2–4 years of age. Lesions grow progressively until puberty when they arrest or regress. Painless symmetrical enlargement at the angles of the mandible and in the maxilla leads to the typical ‘cherubic’ facial appearance. Expansion of the alveolar bone results in irregular spacing and premature loss of teeth and possibly disturbances to a developing dentition. Radiography shows well-defined multilocular radiolucencies in the mandible, but maxillary lesions are less clearly defined. Blood chemistry is normal, although there may be a raised alkaline phosphatase during active growth periods. Histologically, the lesions consist of loose vascular connective tissue with numerous multinucleated giant cells and, as in fibrous dysplasia, there is fibrous replacement of bone (Fig. 44.2). Other fibro-osseous lesions and giant cell lesions of bone (giant cell granuloma, hyperparathyroidism, giant cell tumours) should be excluded. Treatment of cherubism is as for fibrous dysplasia (see also Noonan syndrome, Ch. 44). It tends to regress after puberty.

Chondroectodermal dysplasia (Ellis-van Creveld syndrome). Autosomal-recessive polydactyly and chondrodysplasia.

Chondroma. A benign tumour, rare in the jaws. The anterior maxilla, mandibular symphysis and the coronoid and condylar processes are the most common

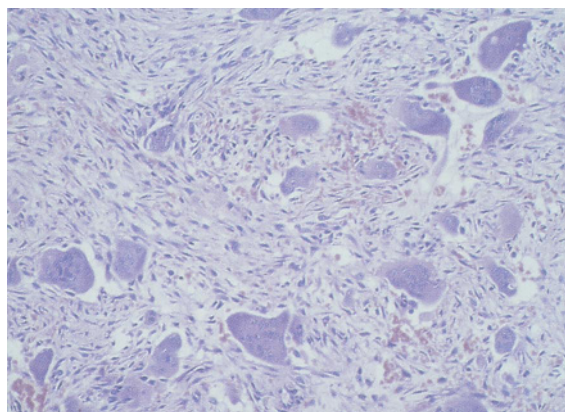


Fig. 44.2 Cherubism

sites. Chondromas are typically found in the elderly and form slow-growing, painless masses. Provided surgical excision of these masses is complete, recurrence is unlikely.

Chondrosarcomas. These tend to affect the elderly and, although isolated cases arise from chondromas, most arise *de novo*. The behaviour is very unpredictable, but many grow rapidly and produce extensive local destruction. Radical surgery, the only means of eradicating the tumour, can be difficult as the edges may not be apparent clinically or radiographically. Multiple local recurrence is common and the prognosis is worse than for osteosarcoma.

Chorea. Consists of a writhing movement of continuous abrupt and intermittent movements that flow randomly from one part of the body to another. Chorea may affect the head and neck, especially in tardive dyskinesia. This is usually a late (hence tardive) complication manifesting as non-random, focal patterned or stereotyped movement induced by dopamine receptor blocking drugs, such as metoclopramide, phenothiazines or butyrophenones, and is somewhat similar to oromandibular dystonia. Senile chorea, including edentulous dyskinesia or orodyskinesia, is found in 16% of the edentulous.

Chronic ulcerative stomatitis. This is similar to erosive lichen planus, with ulcers and erosions affecting mainly the buccal or lingual mucosae, but sometimes the gingivae. The lesions and clinically normal mucosa have a distinct pattern of a particulate stratified squamous-epithelium-specific (SES) antinuclear antibody (ANA) on direct immunofluorescent examination of perilesional tissue, and patients can have circulating ANA. Hydroxychloroquine is effective therapy.

Cleidocranial dysplasia (dysostosis). A rare autosomal dominant condition, or mutation. Clinical features include exaggerated transverse diameter of cranium,

delayed fontanelle closure, multiple wormian bones, frontal and parietal bossing, depressed nasal bridge, maxillary hypoplasia, underdeveloped paranasal sinuses, high arched palate (? cleft), delayed or failed tooth eruption, multiple supernumerary teeth, dentigerous cysts, aplastic or hypoplastic clavicles (shoulders can be approximated), short stature and other skeletal anomalies.

Diagnosis is from the family history and ability to bring together the shoulders; jaw, skull and skeletal radiography.

Management is to leave unerupted teeth alone unless there are complications. Eruption of permanent teeth is retarded and dentigerous cysts are frequently found. Supernumerary teeth are common in cleidocranial dysplasia, especially in the anterior mandible. The crowns of the teeth are normal, but the roots can be short, thin and lack acellular cement. Surgery is often necessary.

Coeliac disease. Coeliac disease is a reaction to gluten, ingestion of which activates immune cells in the small intestine, which trigger inflammation and local damage, disrupting food absorption. Untreated coeliac patients lose weight, develop deficiency syndromes such as anaemia, and experience symptoms such as diarrhoea. Gluten is found in wheat, barley and rye, which means that many dietary staples, such as bread, many breakfast cereals and foods like pizza and pasta, can no longer be eaten.

Congenital epulis. A rare reactive process seen on the alveolus of a neonate.

Constricted pupils. Constricted pupils (miosis) can be caused by sympathetic nerve lesions, cholinergic drugs (e.g. pilocarpine or neostigmine) or opiates (heroin, etc.). Thus, heroin addicts may be recognized by 'pin-point pupils'. Raised intracranial pressure is the most important cause of pupil constriction and is noted when the pupil also becomes non-reactive owing to pressure on the oculomotor nerve. It may occur after head injury, intracranial haemorrhage or brain tumour.

Cranial arteritis (temporal arteritis; giant-cell arteritis).

A febrile, often self-limiting disease, which affects old people and is characterized by painful inflammation of the superficial temporal and other cranial arteries, malaise, weakness, weight loss, anorexia, fever, sweating and a raised erythrocyte sedimentation rate (ESR) (or plasma viscosity). The headache is intense, deep and aching, throbbing in nature and persistent, frequently made worse when the patient lies flat in bed and may be exacerbated or reduced by digital pressure on the artery involved. There may be jaw claudication (pain on chewing) or even pain and necrosis in the tongue. Occasionally the artery may be enlarged and tender. Diagnosis is clinical, supported by a raised ESR, and arterial biopsy, which shows the arterial elastic tissues to be fragmented, with giant cells numerous in

the region of the deranged internal elastic lamina. Management is urgent treatment with systemic corticosteroids (prednisolone), since the retinal artery can be affected and loss of vision may be threatened.

CREST syndrome. Calcinosis, Raynaud's disease, oesophageal involvement, sclerodactyly and telangiectasia (see scleroderma, p. 368).

Cri-du-chat. Short arm of chromosome 5 deletion, resulting in microcephaly, hypertelorism, and laryngeal hypoplasia causing a characteristic shrill cry.

Crystal deposition diseases ('gout'). A term used to encompass diseases that produce crystals in joints (e.g. gout, chondrocalcinosis, secondary gout caused by cytotoxic therapy) including the temporomandibular joint. Gout itself is an uncommon disorder of metabolism in which excessive levels of uric acid in the blood and other body fluids crystallize out in synovial fluid causing acute inflammation. The patient complains of a painful, swollen joint and 'pan-meniscal crepitation' is elicited on movement. Acute attacks are often preceded by a 'binge' of dietary or alcohol excess or 'starvation', trauma or unusual physical exercise, surgery or systemic illness. In chronic gout, tophi are frequently felt in the cartilage of the pinna of the ear. Diagnosis is clinical, but usually confirmed by a leucocytosis, raised erythrocyte sedimentation rate (ESR), raised serum urate level and aspiration biopsy for examination under polarizing light for crystals of urate (or pyrophosphate in pseudo-gout). Radiography is not often particularly helpful, since the appearance resembles osteoarthritis. Treatment must not be restricted just to the local treatment of the TMJ. Non-steroidal anti-inflammatory drugs (NSAIDs) should be started. Colchicine is effective. Gout is usually treated prophylactically with allopurinol. Dietary advice and weight control are also important.

Cystic hygroma. A developmental anomaly of lymphatics presenting as a swelling of the neck seen before the age of 2 years. It may extend into the mediastinum and/or tongue. Cystic hygroma is usually surgically removed.

Cysts. A pathological cavity having liquid, semi-liquid or gaseous contents. It is frequently, but not always, lined with epithelium. Cysts of the jaws mostly arise from odontogenic epithelium, and are relatively common lesions. Non-odontogenic developmental cysts are uncommon and were said to form from entrapment of epithelium during the fusion of embryological processes, but this embryological concept has now been discarded. The lining of these cysts is either stratified squamous epithelium or pseudostratified ciliated columnar (respiratory) epithelium. Non-odontogenic cysts include the following:

- *Nasopalatine or incisive canal cysts* – derived from the vestigial oronasal ducts. They may occur either

within the nasopalatine canal, or in the soft tissues of the palate at the opening of the canal, grow slowly, and may discharge into the mouth giving a salty taste. Radiological examination shows a well-defined, rounded ovoid or occasionally heart-shaped defect in the anterior maxilla. Nasopalatine cysts must be distinguished from a normal large anterior palatine fossa which may be up to 7mm in diameter, and from radicular cysts associated with the maxillary incisors. These cysts should be enucleated and seldom recur.

- *Nasolabial cysts* – soft tissue cysts found within the nasolabial fold. They are lined by respiratory epithelium, and if allowed to grow may distort the upper lip and alar base. Treatment is by simple excision.

Dentinogenesis imperfecta. A rare autosomal-dominant disorder in which the dentine is abnormal in structure and, hence, translucent (Fig. 44.3), and poorly attached to enamel. All teeth are affected, but primary teeth are more severely affected than permanent teeth. In the permanent dentition the teeth that develop first are generally more severely affected than those that develop later. The teeth:

- are translucent
- may vary in colour from grey to blue or brown
- enamel is poorly adherent to the abnormal underlying dentine and easily chips and wears
- crowns are bulbous with pronounced cervical constriction and the roots are short
- fracture easily (there is progressive obliteration of pulp chambers and root canals with secondary dentine)
- periapical radiolucencies are not uncommon.

There are three types:

- Type I (associated with osteogenesis imperfecta): most severe in deciduous dentition; bone fractures; blue sclerae; progressive deafness; caused by mutations in one of several genes.
- Type II (hereditary opalescent dentine): defect equal in both dentitions; caused by mutations in the DSPP gene. A few families with type II have progressive hearing loss in addition to dental abnormalities.



Fig. 44.3 Dentinogenesis imperfecta

- Type III (Brandywine type – first identified in Brandywine, Maryland, USA): associated with occasional shell teeth and multiple pulpal exposures; caused by mutations in the DSPP gene.

Differentiate mainly from amelogenesis imperfecta, tetracycline staining and dentine dysplasia. Management is by restorative dental care.

Denture-induced hyperplasia (denture granuloma; epulis fissuratum). A painless, firm swelling with a smooth pink surface usually in the buccal sulcus related to a lower complete denture, especially anteriorly. Pressure from a denture flange causes chronic irritation and a hyperplastic response. Common, mainly in middle-aged or elderly patients, the diagnosis is clear cut if the lesion is in relation to a denture flange. If ulcerated, it may mimic carcinoma (rarely). Diagnosis is clinical, but excision biopsy may be indicated. The denture flange should be relieved, to prevent recurrence.

Dermatitis herpetiformis. An uncommon chronic skin disorder associated often with gluten-sensitive enteropathy, affecting mainly middle-aged males. Symmetrical papulovesicular eruptions on extensor surfaces. Oral lesions of vesicles and/or desquamative gingivitis, similar to pemphigoid typically follow skin lesions. Biopsy of perilesional tissue, with histological and immunostaining examination are essential to diagnosis, showing IgA deposits at the papillae. Jejunal biopsy often indicated. Dapsone is the main therapy – sulfamethoxypyridazine and sulfasalazine are alternatives. A gluten-free diet can minimize disease activity and can reduce or avoid the need for drugs.

Dermatomyositis. A rare autoimmune disorder that occasionally presents with oral ulcers and erythema of the tongue, palate or gingivae.

Dermoid cyst. A rare developmental cyst that presents as a doughy painless swelling in the midline floor of mouth and needs to be differentiated from ranula and cystic hygroma. Diagnosis is by aspiration, but there is a risk of infection. Management is by surgical removal.

Desquamative gingivitis. A fairly common problem in which the gingivae show chronic desquamation and is a term that denotes a particular clinical picture and not a diagnosis in itself. Many of the patients are middle-aged women. Desquamative gingivitis is mainly a manifestation of:

- mucocutaneous disorders, usually. Most gingival involvement in the vesiculobullous or skin diseases (dermatoses) is related to lichen planus or pemphigoid, but pemphigus, dermatitis herpetiformis, linear IgA disease, chronic ulcerative stomatitis and other conditions may need to be excluded. Most of

these conditions are acquired, but a few are congenital with a strong hereditary predisposition, such as epidermolysis bullosa

- chemical damage, such as reactions to sodium lauryl sulphate in toothpastes
- allergic responses
- drugs
- psoriasis
- pyostomatitis vegetans

Some patients make no complaint, but others complain of persistent gingival soreness, worse when eating spices, or acidic foods, such as tomatoes or citrus fruits. Most patients are seen only when vesicles and bullae have broken down to leave desquamation, and the clinical appearance is thus of erythematous gingivae, mainly labially, the erythema and loss of stippling extending apically from the gingival margins to the alveolar mucosae. The desquamation may vary from mild almost insignificant small patches to widespread erythema with a glazed appearance. In addition to a full history and examination, biopsy examination and histopathological and immunological investigations are frequently indicated.

Conditions which should be excluded include:

- reactions to mouthwashes, chewing gum, medications and dental materials
- candidiasis
- lupus erythematosus
- plasma cell gingivitis
- Crohn's disease, sarcoidosis and orofacial granulomatosis
- leukaemias
- factitial (self-induced) lesions.

The treatment of desquamative gingivitis consists of:

- improving the oral hygiene
- minimizing irritation of the lesions
- specific therapies for the underlying disease where available
- local or systemic immunosuppressive or dapsone therapy, notably corticosteroids.

Corticosteroid creams used overnight in a soft polythene splint may help.

Dilated pupils (mydriasis). Can be caused by parasympathetic lesions affecting the third nerve, Holmes-Adie syndrome, Horner syndrome, anticholinergic drugs (e.g. atropine or similar drugs), sympathomimetic drugs (e.g. adrenaline, cocaine). Users of cocaine or crack cocaine may thus have dilated pupils.

Drug addiction (illegal drug use). This is increasingly common, particularly in urban areas. Addicts in need of a 'fix' will often falsely complain of severe pain or injury. Disturbed behaviour in a drug addict may be caused by withdrawal symptoms and the patient may need compulsory detention. If an addict is admitted

to the ward, contact a licensed psychiatrist for heroin or cocaine to be given for addicts. The most serious problems in the management of addicts include:

- overdose
- withdrawal effects
- behavioural problems (including theft)
- violence
- hepatitis
- HIV infection
- other infections.

Dysarthria. Disordered speech. Normal speech involves a complex series of muscles, particularly the muscles of respiration, larynx, pharynx, palate, tongue and lips and, like all voluntary muscle activity, is under control from higher centres, both pyramidal and extrapyramidal. The act of speaking is a highly coordinated sequence involving articulation and phonation under direct control of the vagus, glossopharyngeal, hypoglossal and facial nerves. Conditions affecting the tongue, palate, pharynx, larynx or these nerves or their central connections, or sensory nerves, can lead to disturbed speech. However, speech also involves a wide range of acquired skills, deficiencies of which impede interpersonal communication irrespective of any other impairment in language usage.

Deranged speech can be due commonly to drugs (including alcohol), CNS disorders as in learning disabilities, cerebral palsy, parkinsonism, delirium or dementia; loss of voice due to laryngeal disease or paralysis (dysphonia); or defects in articulation because of paralysis, rigidity, tissue loss or scarring, or involuntary movements of tongue or palate. The most common oral cause of dysarthria is immobility of the tongue after a lingual block local analgesic injection, trauma to the tongue, scarring, diseases affecting the tongue (such as carcinoma) or foreign bodies (such as in oral piercing). Spastic dysarthria is usually caused by cerebrovascular disease affecting the motor cortex (causing pseudobulbar palsy), extrapyramidal disease, such as parkinsonism, or drugs, such as phenothiazines; basal ganglia disease causes choreic dysarthria; cerebellar disease causes ataxic dysarthria. Alcohol also has this effect. Paralytic dysarthria is less common, but may be caused by medulla oblongata disease (bulbar palsy), cranial nerve lesions affecting nerves VII, IX, X, XI or XII, myopathies, such as myasthenia gravis. Patients with persistent dysarthria should be referred for a neurological opinion.

Dyskinesias. Abnormal movements of the tongue or facial muscles, sometimes with abnormal jaw movements, bruxism or dysphagia. Involuntary tongue protrusion and retraction, and facial grimacing are common dyskinesias. They differ from dystonias mainly in that muscle spasm is less prominent, but

they may be difficult to differentiate clinically. They are usually caused by extrapyramidal disease, such as athetosis, or drugs (e.g. phenothiazines, tricyclics, oral contraceptive, metoclopramide, antipsychotics). Most dyskinesias resolve within 4 weeks of stopping any causal medication. If not, treat with anti-parkinsonian drugs (e.g. benzhexol), baclofen, benzodiazepines, dopamine depletors (reserpine or tetrabenazine), calcium channel blockers, clozapine, buspirone, α -adrenergic agonists, vitamin E or botulinum toxoid.

Dysphasias. Disturbances of language use (or aphasias), and may be caused by brain disease, such as stroke or after head injury, in which there is loss of production and comprehension of speech and language.

Dystonias. A group of uncommon neurological diseases characterized by abnormal movements, such as sustained and patterned contractions producing abnormal postures, repetitive twisting or squeezing.

Epidermolysis bullosa. A rare genetically-determined disorder related to a defect in the epidermolysis bullosa antigen in the epithelial basal lamina, leading to blistering after trauma, and scarring, which may cause severe disability, such as limb deformities, microstomia, ankyloglossia and trismus. Enamel hypoplasia may be seen. Diagnosis is from the family history and a biopsy to exclude other blistering diseases. Management includes careful attention to oral hygiene. Trauma should be minimized, and drugs such as phenytoin may help reduce the blistering.

Epidermolysis bullosa acquisita. A rare non-inherited chronic mechano-bullous disease characterized by autoantibodies directed against type VII collagen. Clinically, bullae are frequently induced after mechanical irritation. The diagnosis should be made on the history, clinical features, histopathological, direct and indirect immunofluorescent examination. Biopsy of perilesional tissue, with histological and immunostaining examination are essential to the diagnosis. Topical corticosteroids effectively control gingival lesions. Systemic corticosteroids alone or in association with immunosuppressive agents and dapsone are suggested treatments.

Epulis. An epulis is the term given to a localized gingival swelling (Fig. 44.4). Epulides normally arise interdental and most are pyogenic granulomas or fibrous lumps.

Exfoliative cheilitis (tic de levres). An uncommon condition affecting the lip vermilion, characterized by continuous production and desquamation of unsightly, keratin scales which, when removed, leave a normal lip beneath (Fig. 44.5). The aetiology is unknown, but some cases may be factitious.



Fig. 44.4 Epulis

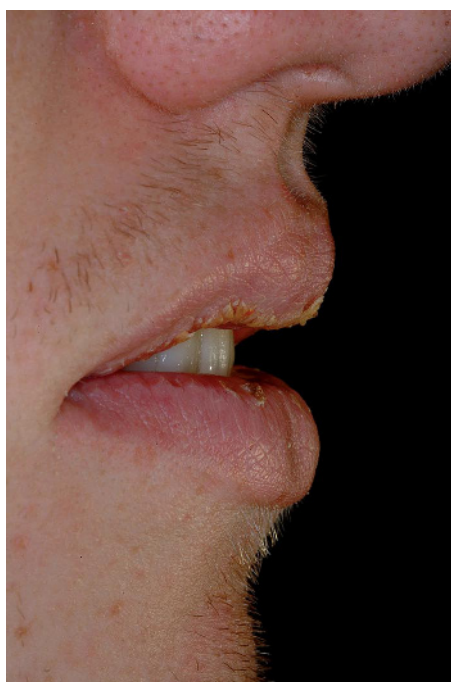


Fig. 44.5 Exfoliative cheilitis

Familial holoprosencephaly. Congenital malformation of the forebrain and midface: microphthalmia, hypopituitarism and hypertelorism.

Fibro-osseous lesions. A group of disorders of unknown aetiology, composed of fibrous and ossified tissue. The main disorders include Paget's disease of bone, fibrous dysplasia and cherubism and the ossifying fibroma.

Fibrous dysplasia. A disorder characterized by the replacement of an area of bone with fibrous tissue. Mutations in signalling protein gene *GNAS 1* may be involved. The process typically starts in childhood and, as the skeleton matures, the lesions progressively ossify. As skeletal growth ceases, the lesion stabilizes. Three types of fibrous dysplasia (FD) are recognized:

- *Monostotic* (MFD), in which there is a single lesion in only one bone.
- *Polyostotic* (PFD), in which several lesions are present in one or more bones.
- *McCune-Albright syndrome*, PFD plus cutaneous pigmentation (cafe-au-lait type) on the same side as the bony lesion, and precocious puberty (see p. 337).

Fibrous dysplasia usually presents as a painless bony hard swelling, most often in the maxilla or adjacent bones. The maxillary sinus is often involved, when there may be encroachment on the orbit (causing proptosis) and nasal cavity (causing obstruction). Expansion of the alveolar bone leads to disruption of occlusion, displacement of teeth and possibly failure of eruption of teeth. Lesions appear to stabilize with skeletal maturation.

Radiographically, there is either a translucent cystic appearance in the affected bone, or mottled opaque areas likened to ground glass. The lesions are often ill-defined and may extend to, but not cross, suture lines. Serum calcium and phosphate levels are normal but, in many, the serum alkaline phosphatase level is high and urinary hydroxyproline is increased (findings similar to those in Paget's disease). Microscopically, the lesion consists of fibrous tissue that replaces the normal bone and gives rise to osseous trabeculae by metaplasia (Fig. 44.6). The osseous tissue is composed of irregular ('Chinese characters') trabeculae of woven bone lined by osteoblasts. Focal degeneration of fibrous tissue accounts for the cystic spaces seen macroscopically. The treatment of choice to correct any cosmetic defect is conservative surgery, preferably after the cessation of normal skeletal growth. The lesion is not radio-sensitive; irradiation may cause sarcomatous change.

Fibrous lump or nodule ('fibroepithelial polyp'). A pedunculated or broadly sessile, sometimes ulcerated, hard or soft, lump seen mainly on the buccal mucosa. It is termed 'epulis' if on the gingival margin. It is common and is probably caused by chronic irritation causing fibrous hyperplasia. Excision biopsy helps differentiate it from any other soft tissue tumour.

Fissured lip. Lip fissures may appear especially where there is exposure to adverse environments (Fig. 44.7), or where the lip swells as in Down syndrome or cheilitis granulomatosa.

Fissured (plicated or scrotal) tongue. An extremely common genetic condition, the dorsum has deep irregular fissures, but is normally papillated (Fig. 44.8). A fissured tongue may also be seen in Down syndrome or Melkersson-Rosenthal syndrome. There are associations with erythema migrans in particular. The diagnosis is usually clear cut. The lobulated tongue of Sjögren syndrome must be differentiated.

Fluorosis. The condition of enamel defects caused by high levels of fluoride. High levels in drinking water are uncommon in the developed world, but are

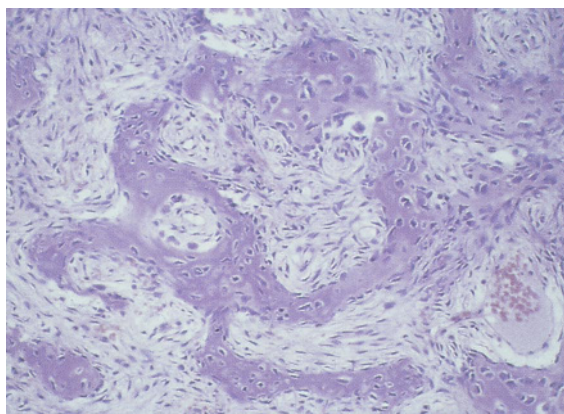


Fig. 44.6 Fibrous dysplasia – Chinese characters



Fig. 44.8 Fissured tongue



Fig. 44.7 Fissured lip



Fig. 44.9 Severe fluorosis

particularly common in parts of the Middle East, India and Africa. Fluorosis affects many teeth:

- *Mildest form:* white flecks or spotting or diffuse cloudiness.
- *More severe form:* yellow-brown or darker patches.
- *Most severe form:* yellow-brown or darker patches, sometimes with pitting (Fig. 44.9).

Diagnosis is from history, clinical appearance and data about fluoride content of drinking water. It is necessary to differentiate from amelogenesis imperfecta and tetracycline staining. Management of severe forms is by the use of veneers or crowns.

Foliate papillitis. The foliate papillae are found on the posterolateral border of the tongue, at the junction of the anterior two-thirds with the posterior third. The size and shape of the foliate papillae are variable and occasionally they swell if irritated mechanically or if there is an upper respiratory infection, and this is termed 'foliate papillitis'. Located at a site of high predilection for lingual cancer, they may give rise to unnecessary concern about cancer.

Furred tongue. Coating of the tongue is quite commonly seen in healthy adults, particularly in edentulous patients, those who are on a soft, non-abrasive

diet, those with poor oral hygiene, or those who are fasting. The coating in these instances appears to be of epithelial, food and microbial debris, which collects since it is not mechanically removed. Indeed, the tongue is the main reservoir of some microorganisms, such as *Candida albicans* and some *Streptococci*. The tongue may be coated with off-white debris in many illnesses, particularly febrile diseases, xerostomia and ill patients – especially those with poor oral hygiene or who are dehydrated. The history is important to exclude a congenital or hereditary cause of a white lesion or candidosis. The clinical appearances may strongly suggest the diagnosis, but investigations are often required if the white lesion does not scrape away from the mucosa with a gauze. Biopsy may then rarely be indicated. Treatment is of the underlying cause.

Giant cell granuloma. The central giant cell granuloma is an uncommon lesion only seen in the tooth-bearing regions of the jaws, most commonly in the mandible and typically in the second and third decades. The true nature of these lesions is unknown but, as they are invariably destructive, the term 'reparative' giant cell granuloma would appear to be inappropriate. Lesions may be symptomless

or simulate a malignant neoplasm clinically and radiographically. Occasionally, the lesion erodes through the cortical bone where it presents as a domed, purplish submucosal swelling. Radiography shows an ill-defined area of radiolucency and there may be resorption of the roots of related teeth. Microscopy shows multinucleated giant cells irregularly distributed in a cellular stroma of plump, spindle-shaped cells which is often highly vascular. There may be areas of new and old haemorrhage with haemosiderin pigment deposition. These microscopic features are indistinguishable from the focal lesions of hyperparathyroidism, which can only be excluded by the appropriate serological tests (calcium and phosphate levels and alkaline phosphatase). Although central giant cell granulomas may recur following curettage, they virtually never metastasize.

Gingival bleeding. This is usually explained by the presence of gingivitis. However, unexplained bleeding can be due to thrombocytopenia (e.g. in leukaemia, HIV disease, idiopathic thrombocytopenic purpura, myelodysplastic syndromes) or occasionally warfarin, other drugs or blood clotting defects.

Glossitis. The term given when the tongue is sore or, more appropriately, when the dorsum of tongue becomes depapillated and red. Causes include anaemia, vitamin or iron (haematinic) deficiency, chemotherapy or radiation therapy, or infection, such as candidiasis. Glossitis in haematinic deficiency states, is seen mainly in:

- malabsorption states
- pernicious anaemia
- chronic bleeding from the gastrointestinal or genitourinary tract
- vegans
- dietary faddists
- poor socioeconomic circumstances (deficiencies of vitamins of the B group other than B₁₂ are an occasional cause of glossitis, mainly seen in chronic alcoholics or in those with malabsorption or starvation).

The tongue may appear completely normal or there may be:

- linear or patchy red lesions: especially in vitamin B₁₂ deficiency.
- depapillation with erythema: in deficiencies of iron, folic acid or B vitamins lingual depapillation begins at the tip and margins of the dorsum, but later involves the whole dorsum (bald tongue).

Various other patterns are described, in deficiencies of:

- riboflavin: papillae enlarge initially, but are later lost

- niacin: red, swollen, enlarged 'beefy' tongue
- pyridoxine: swollen, purplish tongue.

There may also be:

- pallor
- burning mouth syndrome
- ulceration
- angular stomatitis.

Differentiate from erythema migrans, lichen planus and acute candidiasis. As sore tongue can be the initial symptom of iron, folate or vitamin B₁₂ deficiency and can precede any haemoglobin fall, a full blood picture with assays of iron (serum ferritin), vitamin B and folate are essential. Biopsy is rarely indicated. Replacement therapy should be instituted after the underlying cause is established and rectified.

Glossopharyngeal neuralgia. A rare condition in which pain with all the characteristics of trigeminal neuralgia is experienced in the posterior tongue, fauces, pharynx and sometimes beneath the angle of the mandible. Treatment is with carbamazepine or, in intractable cases, posterior fossa neurosurgery.

Glycogen storage diseases. Inborn errors of metabolism. Type 1B results in neutropenia and periodontal destruction.

Gonorrhoea. Infection with *Neisseria gonorrhoea* in the mouth is uncommon or rarely recognized. Pharyngitis may occur after orogenital or oroanal contact. Swab for culture and sensitivity. Treat with amoxicillin or ciprofloxacin.

Granular cell myoblastoma (granular cell tumour). A fairly common hamartoma, the origin of which is unclear. Presents as a pedunculated or occasionally sessile swelling on the gingivae, tongue, buccal mucosa or lip. It should be excised. Histology shows a pseudoepitheliomatous appearance, but it is benign.

Haemangiomas. Vascular malformations (hamartomas) that are red, purple or blue, painless, soft and sometimes fluctuant and usually blanch on pressure. Most appear in infancy, but about 15% develop later. Haemangiomas are common on the tongue, lip vermillion, or buccal mucosa (Fig. 44.10). Diagnosis may be assisted by aspiration, ultrasonography, radiography, angiography, magnetic resonance imaging (MRI), and MRI-angiography. Differentiate from lymphangioma, telangiectasia, purpura, Kaposi sarcoma and epithelioid angiomatosis. Management may be active, with removal of the haemangioma, or simple observation (since some 50% regress spontaneously in childhood). Cryosurgery or laser (Nd-YAG, carbon dioxide, pulsed tuneable dye or copper vapour) are the main treatments. Alternatively, sclerosant injection (boiling water, absolute alcohol, sodium tetradecyl sulphate, sodium morrhuate or ethanolamine oleate), compression sutures (Popescu) or (rarely) arterial embolisation are used.



Fig. 44.10 Haemangioma in the lip

Haemangiopericytoma. A rare tumour arising from pericytes; there are benign and malignant forms.

Haemochromatosis. An inborn error of iron overload which may cause diabetes, cardiomyopathy and mucocutaneous brown pigmentation or salivary swelling

Haemophilia. Haemophilia A – deficiency of blood clotting factor VIII.

Hairy leukoplakia. HIV-infected and other severely immunocompromised patients may develop white oral lesions with a vertically corrugated or 'hairy' surface ('hairy leukoplakia') which usually affects the lateral margins or dorsum of tongue. Epstein-Barr virus may be implicated.

Hand, foot and mouth disease. A common Coxsackie virus infection (usually A16; rarely A5 or A10), with an incubation of 2–6 days occurring in small epidemics, in children. Clinical features include oral ulcers resembling herpetic stomatitis, but affecting labial and buccal mucosa, no gingivitis, mild fever, malaise, anorexia, rash (red papules that evolve to superficial vesicles in a few days, found mainly on palms and soles). Diagnose from the clinical features. Serology is confirmatory, but rarely required. Differentiate from herpetic stomatitis, chickenpox. Management is symptomatic (see herpes simplex, Ch. 31).

Hemifacial spasm. A spasm of the angle of the mouth or the eyelid, worse towards evening. Usually idiopathic, it may be caused by a vascular anomaly affecting the vertebrobasilar vessels (dolichoectasia) causing pressure on the facial nerve. Some cases herald a cerebellopontine angle lesion or other lesion irritating the facial nerve. CT or MRI are indicated. Botulinum toxin injections into the affected muscles may give relief. Anticholinergics, phenytoin, carbamazepine or benzodiazepines may help. Rarely are myectomy or microvascular decompression indicated.

Hemimasticatory spasm is similar, but affects the masticatory muscles and may be associated with progressive hemifacial atrophy. It also often responds to botulinum toxin.

Hereditary gingival fibromatosis (HGF). Gingival enlargement begins in puberty, is painless, slowly progressive and dependent to a great extent on the oral hygiene. The hyperplastic tissues are usually firm to palpation. It is not unusual for the fibromatosis to completely cover the teeth.

Symmetrical fibromatosis of the tuberosities is typically bilateral and presents as a generalized, soft, smooth-surfaced, painless enlargement of the tissues over the posterior maxillary alveolus.

The most common form of HBF (HGF-1) maps to 2p21 and is caused by mutation in the *SOS1* (*Son of sevenless-1*) gene (a guanine nucleotide-exchange factor that mediates the coupling of receptor tyrosine kinases to Ras activation) or to chromosome 5q13-q22. An autosomal dominant form may be associated with hypertrichosis. Syndromic forms (e.g. Rutherford, Cross, Laband, Ramon syndromes) have other inheritance.

Herpangina. A Coxsackie virus infection (A7, A9, A16; B1, B2, B3, B4 or B5) or echovirus (9 or 17) with an incubation period of 2–6 days. Clinical features include oropharyngeal ulcers, no gingivitis, cervical lymphadenitis (moderate), fever, malaise, irritability, anorexia, vomiting, but no rash. Diagnose from clinical features. Serology (theoretically) is confirmatory. Differentiate from herpetic stomatitis and chickenpox. Manage symptomatically.

Holoprosencephaly. A common developmental defect affecting the neural crest cells populating the frontonasal mass and the forebrain, with the associated appearance of midface defects.

Human papilloma viruses. DNA epitheliotropic viruses which most commonly produce papillomas, but are also implicated in skin warts and venereal warts (condyloma acuminatum), and rare disorders, e.g. focal epithelial hyperplasia (Heck's disease). A higher prevalence is seen in patients with sexually transmitted infections or who are immunocompromised, as in HIV/AIDS:

- Papillomas are uncommon in the mouth, but typically seen on the fauces, soft palate or tongue, usually less than 5mm diameter and with whitish filiform projections.
- Warts are rare in the mouth:
 - verrucae vulgaris, usually transmitted from skin lesions, are found predominantly on the lips
 - condyloma acuminata, transmitted from genital or anal lesions, are found mainly on the tongue or palate.

Diagnose by biopsy to differentiate from other tumours. Manage with podophyllum or imiquimod, excision, laser, or electro- or cryosurgery.

Hypercementosis. This may arise in:

- occlusal trauma
- overerupted non-opposed tooth

- periapical infection
- paget's disease
- acromegaly
- idiopathic.

Hyperparathyroidism *Primary hyperparathyroidism* – usually due to a parathyroid adenoma, carcinoma or hyperplasia of parathyroid tissue or ectopic production of parathyroid hormone (PTH) (e.g. by tumours of lung or kidney). May also rarely occur in association with adenomas of other endocrine glands (the multiple endocrine adenoma syndromes). Serum calcium levels are raised, as usually is the alkaline phosphatase. Phosphate levels are reduced. The clinical features are the direct result of either excess PTH or calcium, and particularly include renal stones, bone lesions, polyuria and abdominal pain ('stones, bones and abdominal groans'). Anorexia and psychoses are not uncommon:

- *Secondary hyperparathyroidism* – usually the consequence of renal disease in which low serum calcium as a consequence of impaired renal production of dihydroxycholecalciferol induces increased parathyroid activity, and eventually hyperplasia of the parathyroid glands. Secondary hyperparathyroidism may also follow malabsorption syndromes. Calcium levels are usually normal or low.
- *Tertiary hyperparathyroidism* – a consequence of chronic overstimulation of the gland in secondary hyperparathyroidism, which rarely leads to neoplastic change in the parathyroids, which then escape the normal control of serum calcium.

Oral manifestations of hyperparathyroidism include reduced bone density (the outlines of the maxillary antrum, inferior dental canal and inferior border of the mandible can become less distinct), loss of the lamina dura, root resorption and radiolucencies (particularly of the mandible). The radiolucent lesions are either areas of high osteoclastic activity or giant cell lesions. The giant cell lesions can present intraorally as epulides. Hyperparathyroidism is managed by excision of the neoplastic or hyperplastic parathyroid tissue. In the secondary and tertiary disorders, treatment of the underlying disorder is also required.

Hypodontia. A reduction in the number of teeth. The teeth most commonly missing are third molars and maxillary lateral incisors, followed by mandibular and maxillary second premolars. It may be associated with microdontia. If >6 teeth missing, the term oligodontia is sometimes used. Anodontia is total absence of the dentition. A genetic trait, ectodermal dysplasia should be considered.

Hypoparathyroidism. Usually caused by damage to, or loss of, parathyroid tissue during neck surgery (e.g.

thyroidectomy). It may also arise rarely as a familial disorder (idiopathic hypoparathyroidism) or very rarely as a consequence of *in utero* damage when it is associated with cellular immunodeficiency (CATCH 22 syndrome: p. 349). The major clinical features are related to the low serum calcium levels. Tetany (hyperexcitability of muscles) is the most obvious and disturbing feature and can lead to laryngeal spasm. Hypoparathyroidism frequently causes paraesthesia about the mouth. Tapping the skin over the facial nerve can elicit involuntary twitching of the muscles of the upper lip or ipsilateral side of face (Chvostek's sign). Hypoparathyroidism can cause enamel hypoplasia of developing teeth and delayed tooth eruption. Treat with hydroxycholecalciferol.

Pseudohypoparathyroidism is a rare condition in which PTH is secreted normally, but the tissue receptors are unresponsive. The features are similar to those of hypoparathyroidism, plus a tendency to short stature and small fingers, but no dental manifestations.

Hypophosphatasia. A rare genetic defect in alkaline phosphatase, causing cemental aplasia or hypoplasia and tooth mobility and early loss. Serum alkaline phosphatase is decreased with increased vitamin B6 and increased urinary phosphoethanolamine.

Hypoplasminogenaemia. A rare genetic defect in plasminogen. Manifestations include swollen, painless, nodular and ulcerated gingivae covered with a yellowish-pink pseudomembrane, and ligneous conjunctivitis.

Idiopathic bone necrosis. An unusual disorder in which a small portion of bone, typically of the mylohyoid ridge, undergoes spontaneous necrosis and sequestration with pain and ulceration.

Impetigo contagiosa. A highly contagious skin infection with streptococci (group A). Uncommon, and seen mainly in underprivileged children (aged 2–6 years), lesions spread by touch to several areas. Clinical features include papules which change into vesicles surrounded by erythema then multiple pustules with golden crusts. Regional lymphadenitis is sometimes seen, but systemic symptoms are rare. Diagnosis is clinical together with culture of pus. On lips, herpes labialis is the prime differential diagnosis, but other vesiculobullous diseases should also be excluded. Management is with antibiotics. If there is no systemic toxicity, use chlortetracycline cream. If there are systemic symptoms, oral flucloxacillin should be used.

Staphylococcus aureus phage type 71 causes bullous impetigo, a severe form with fever.

Juvenile hyaline fibromatosis. A hereditary condition which may involve the gingiva, with swelling and a prominent PAS-positive matrix of chondroitin sulfate.

Leiomyoma. A rare benign tumour from smooth muscle.

Leukaemia. A malignant proliferation of leucocytes. Common oral manifestations in leukaemia include lymphadenopathy, bleeding, petechiae, gingival swelling, ulceration. Other findings include sensory changes (particularly of the lower lip), extrusion of teeth, painful swellings over the mandible, parotid swelling (Mikulicz syndrome), fungal infections, and predisposition to herpesvirus lesions. Diagnose by a blood film, white cell count (raised), differential count (shows blasts), platelet count (reduced) and bone marrow biopsy. Treat mainly by chemotherapy. Oral hygiene should be carefully maintained with chlorhexidine mouth rinses and a soft toothbrush. Prophylactic antifungal and antiviral therapy is also indicated. Many chemotherapeutic agents can cause oral ulceration. Methotrexate is a major offender, but ulceration may be prevented or ameliorated by concomitant intravenous administration of folinic acid ('leucovorin rescue') or topical folinic acid (see Ch. 41). There are several types of leukaemia:

- *Acute lymphoblastic leukaemia* (ALL). The most common leukaemia of childhood, it has a peak incidence at 3–5 years of age. Malignant lymphoblasts proliferate and infiltrate the viscera, skin and central nervous system. Marrow infiltration causes granulocytopenia (predisposing to infections), thrombocytopenia (causing a bleeding tendency) and anaemia ('there is no leukaemia without anaemia').
- *Acute myeloblastic leukaemia* (AML). The most common acute leukaemia of adults. Features are similar to acute lymphoblastic leukaemia, but central nervous system involvement is rare.
- *Chronic lymphocytic leukaemia* (CLL). The most common chronic leukaemia. It mainly affects the elderly. Some patients are asymptomatic, while in others there is fever, weight loss, anorexia, haemorrhage and infections. Lymph node enlargement is early and may be detected in the neck. CLL may need no treatment.
- *Chronic myeloid leukaemia* (CML). This is characterized by proliferation of myeloid cells in the bone marrow, peripheral blood and other tissues, and mainly affects those over 40 years of age. Splenomegaly and hepatomegaly are common. Anaemia, weight loss and joint pains are not uncommon. The prognosis is variable, but sooner or later there is transformation to an acute phase similar to AML (blast crisis).

Leucocyte adhesion deficiency (LAD). Autosomal recessive defect in beta integrins (Mac-1 or P150,95), impeding polymorphonuclear leucocyte adhesion and migration. Presents with infections and juvenile periodontitis.

Leucoedema. Not a mucosal disease – simply the description of very faint whitish lines in some normal buccal mucosae, seen very often in people of African origins. The whitish lines disappear if the mucosa is stretched (a diagnostic test).

Leucopenia. This may result from viral infections (especially HIV), drugs, irradiation, or can be idiopathic. There is a predisposition to infections, and persistent ulcers lacking an inflammatory halo. Diagnose by a full blood picture and bone marrow biopsy. Manage by improving oral hygiene; antimicrobials as necessary.

Linea alba (occlusal line) A simple line of frictional keratosis seen in the buccal mucosae, horizontally aligned with the occlusal surfaces of the teeth, sometimes with small vertical lines coincident with the interdental areas. More prominent where there is bruxism or clenching. No treatment is required. The tongue is often scalloped also.

Linear IgA disease and chronic bullous dermatosis of childhood. These are subepithelial immune blistering diseases in which there is linear deposition of IgA autoantibodies at the epithelial basement membrane zone:

- *Linear IgA disease* (adults) – oral lesions that mimic mucous membrane pemphigus, in particular oral vesicles and ulcers.
- *Chronic bullous dermatosis* (childhood) – similar oral lesions and sometimes scarring.

Diagnosis is by biopsy of perilesional tissue, with histological and immunostaining. Most patients respond to high-dose prednisolone, dapsone or sulfonamides.

Lingual thyroid. Ectopic thyroid tissue in the tongue.

Lingual varicosities. A fairly common condition of older people in which distended blood vessels are seen on the tongue ventrum (Fig. 44.11). No treatment necessary.

Lipoma. A rare benign tumour of adipose tissue, presenting as a slow-growing, yellowish, soft, semifluctuant, painless mass usually in the buccal mucosa. Diagnose by biopsy; manage by excision.

'Loose bodies'. Hydroxyapatite crystal deposits within the temporomandibular joint space may be seen in osteochondritis dissecans (1–3 'loose bodies'); osteoarthritis (1–10 'loose bodies'); chip fracture of the articular surface (1–3 'loose bodies'); or synovial chondromatosis (50–500 'loose bodies'); and can cause pain. If the pain does not respond to conservative treatment, joint exploration may be needed.

Lupus erythematosus. A rare autoimmune disease seen usually in females. The aetiology is unclear, but drugs, hormones and viruses may contribute in genetically predisposed persons:

- Discoid lupus erythematosus (DLE): oral lesions are seen in up to 25% of those with cutaneous DLE,



Fig. 44.11 Varices

mainly in the buccal mucosa, gingiva and lip. Characteristic features include central erythema, white spots or papules, radiating white striae at margins and peripheral telangiectasia.

- Systemic lupus erythematosus (SLE): oral lesions like those in DLE, but usually more severe ulceration. SLE may also be associated with Sjögren syndrome and, rarely, temporomandibular joint arthritis.

Diagnose by biopsy, blood picture and autoantibodies, especially crithidial (double-stranded DNA). Antinuclear factors are present in SLE, not in DLE. Biopsy shows the lupus band test with basement membrane zone deposits of IgG/IgM. Differentiate from lichen planus, leukoplakia (keratosis), galvanic-induced white lesions and carcinoma. Management includes:

- DLE: topical corticosteroids, cryosurgery or excision of localized lesions; there is a small predisposition to carcinoma.
- SLE: systemic steroids, azathioprine, chloroquine or gold.

Lymphangioma. A hamartoma or benign neoplasm of lymphatic channels that presents as a colourless, sometimes finely nodular soft mass. Bleeding into lymphatic spaces causes sudden purplish discolouration. If in the tongue and extensive, it is a rare cause of macroglossia. If in the lip, it is a rare cause of macrocheilia. Diagnosis can be confirmed, if necessary, by excision biopsy.

Lymphomas (See also Burkitt's lymphoma, Hodgkin's disease and non-Hodgkin's lymphoma.) Malignant tumours that originate in lymph nodes and lymphoid tissue, they can originate from any type of lymphocyte, but usually from B cells. HIV/AIDS and immunosuppression predispose. Painless enlarged cervical lymph nodes are the initial complaint in 50% of cases, but a lymphoma may occasionally produce primary or secondary oral tumours appearing as swellings, often of the pharynx, palate, tongue, gingivae or lips. Involvement of Waldeyer's ring is common in non-Hodgkin's lymphomas.

Patients with lymphoma develop a secondary immunodeficiency, when herpes zoster, herpetic stomatitis and oral candidiasis may be seen. Diagnose from

clinical findings (generalized lymph node enlargement and hepatosplenomegaly), radiography (hilar and abdominal lymph node enlargement), lymphangiography, biopsy (lymph node or lesional). Treatment is chemotherapy.

Malignant melanoma. A malignant tumour of melanocytes, usually presenting as a heavily pigmented (occasionally non-pigmented) macule or, later, a nodule or ulcer. It may spread across several centimetres. The palate is most frequently affected, with spread to regional lymph nodes and then bloodstream. To differentiate naevi and other pigmented lesions, diagnosis is by wide excision biopsy. However, if melanoma clinically is a significant possibility, the patient should be referred for immediate surgery.

Masseteric hypertrophy. May result from repeated jaw clenching or bruxism.

Measles. A common childhood exanthem, caused by measles virus, with an incubation of 7–14 days. Features include Koplik's spots (small white buccal mucosal spots during prodrome), rash (maculopapular), conjunctivitis, runny nose, cough, fever, malaise and anorexia. Diagnose from clinical features; a rising antibody titre is confirmatory. Differentiate from thrush and Fordyce spots (not in children). Management is symptomatic.

Metastatic tumours in the jaws. The jaws are not a common site for clinically obvious metastases but it is probable that subclinical secondary deposits are not rare. The mandible is involved four times as frequently as the maxilla, especially in the premolar and molar region. Symptoms are pain and swelling, anaesthesia, hypoaesthesia or paraesthesia, loosened teeth, and occasionally pathological fracture. In up to one-third of patients, the jaw lesions are the first manifestation of tumour. The most common sites of the primary neoplasm are bronchus, breast, kidney and thyroid gland – when metastases are usually destructive and osteolytic. Prostate metastases tend to be osteoblastic and may be confused radiographically with chronic osteomyelitis, Paget's disease or cemental lesions.

Meth mouth. A term that applies to teeth affected by problems that can include caries, attrition, cracks and erosion attributed to heavy methamphetamine use caused by a combination of drug-induced xerostomia, poor oral hygiene, frequent consumption of carbonated beverages, and tooth grinding and clenching.

Migraine. A recurrent headache, affecting women especially, it appears related to 5-HT (serotonin) release, cerebral arterial dilatation and increased midbrain periaqueductal grey matter metabolic activity (the endogenous pain control pathway). Attacks may be precipitated by stress, alcohol, various foods such as ripe bananas or chocolate, or the contraceptive pill. Preceding warning symptoms (an aura) of visual, sensory, motor or speech disturbances. Visual phenomena

often of zig-zag coloured lights (fortification spectra) or transient visual defects. Headache is severe, usually unilateral (hemicranial) and lasts for hours or days. Photophobia, nausea or vomiting may occur. The number, frequency and intensity of attacks decrease with increasing age and spontaneous remissions are not uncommon. Diagnosis is clinical. Management is aspirin or paracetamol (acetoaminophen), or lysine acetylsalicylate with metoclopramide in acute attacks. Patients usually prefer to lie in a quiet, dark room. Other treatments are directed at 5-HT receptors or uptake by blood platelets. Dihydroergotamine (interacts with 5-HT receptors) or sumatriptan (or other triptan-5-HT agonists which stimulate 5-HT receptors; see migrainous neuralgia, below), tricyclic antidepressants or phenelzine may also help intractable migraine. Prophylaxis with cyproheptadine, pizotifen, propranolol, tricyclics or calcium channel blockers.

Migrainous neuralgia. (Cluster headaches; histamine cephalgia; Sluder's headaches.) Pain defined by the International Headache Society as unilateral excruciatingly severe attacks of pain in the ocular, frontal and temporal areas, recurring in separate bouts with daily or almost daily attacks for weeks or months usually with ipsilateral lacrimation, conjunctival injection, photophobia and nasal stuffiness and/or rhinorrhoea. Less common than migraine, males are mainly affected and attacks often begin at about middle age. Generally, attacks last less than 1 hour (usually 30–45 minutes), commence and often terminate suddenly, and often awaken the patient at night or in the early morning hours (2–3 a.m.). There is vasodilatation in the extracranial carotid arteries and increased hypothalamic metabolic activity. Attacks are sometimes precipitated by hypoxaemia in REM sleep or at high altitudes, or where there is vasodilatation induced by alcohol, histamine or nitroglycerin. Diagnosis is clinical but, as similar symptoms may be related to tumours around the cavernous sinus and craniospinal junction, CT and/or MRI are indicated. Manage with oxygen inhalations, and a triptan, e.g. sumatriptan. Prophylaxis includes lithium, verapamil, nifedipine, diltiazem or ergotamine.

Mixed connective tissue disease. Characterized by anti-RNP autoantibodies, this may present with xerostomia, trigeminal neuropathy, oral ulceration or Sjögren syndrome.

Mucocele. Cystic lesions of minor salivary glands. Most are caused by trauma to the duct, leading to mucus extravasation. This type of mucocele is not, however, lined by epithelium, and, therefore, is not a true cyst. Occasional mucoceles are caused by saliva retention. Most mucoceles appear in the lower labial mucosa, buccal mucosa or ventrum of tongue. They are fluctuant bluish lesions and either resolve spontaneously or can be excised or removed with cryosurgery.

Minor salivary gland outlet obstruction is most commonly encountered when a mucocele is present, although smoking and its accompanying nicotinic stomatitis produces transient palatal minor gland outlet obstruction also.

Superficial mucoceles may be seen in lichen planus.

Multiple Endocrine Adenoma (MEN) syndrome.

There are three main types:

- MEN 1: parathyroid tumours, pancreatic tumours, and pituitary tumours.
- MEN 2a: medullary thyroid cancers (MTC), pheochromocytoma, and parathyroid tumours.
- MEN 2b: medullary thyroid cancers, pheochromocytoma and neuromas.

There are specific *genetic* causes for each of the three types and any particular MEN family will have only **one** type of MEN.

Mumps (acute viral sialadenitis; epidemic parotitis).

A common acute viral disease which principally affects the parotid salivary glands. Mumps is:

- caused by an RNA paramyxovirus (the mumps virus)
- transmitted by direct contact or by droplet spread from saliva
- characterized by a longish incubation period of 2–3 weeks
- followed by immunity to further attacks.

Typically the patient suffers an acute onset of:

- painful salivary swelling (parotitis), usually bilaterally, although in the early stages only one parotid gland may appear to be involved. There is no significant xerostomia. In approximately 10% of cases the submandibular glands are also affected; rarely, these may be the only glands involved. Generally, the salivary swelling persists for about 7 days and then gradually subsides
- trismus
- fever
- malaise.

Mumps less commonly and mainly in adults has extrasalivary manifestations involving organs other than the salivary glands, including:

- orchitis; ensuing infertility is rare
- pancreatitis
- meningoenzephalitis
- rarely, oophoritis and thyroiditis; ensuing infertility is rare.

The diagnosis is on clinical grounds, but confirmation, if needed, is by demonstrating a fourfold rise in serum antibody titres to mumps S and V antigens between acute serum and convalescent serum taken 3 weeks later. Other viruses can rarely produce

parotitis. No specific antiviral agents are available. Treatment is symptomatic involving:

- analgesics
- adequate hydration
- reducing the fever.

Patient isolation for 6–10 days may be advisable since virus is in saliva during this time.

Muscular dystrophies. Genetic myopathies which may cause facial muscle weakness:

- **Facioscapular humeral muscular dystrophy:** an autosomal-dominant condition, which progresses slowly. A dull-looking face which has no expression in conversation and can only just straighten the lips for a smile is characteristic, especially if seen with absence of blinking. As the name implies, the shoulders and upper part of the arms are also involved.
- **Dystrophia myotonica;** an autosomal-dominant condition. The first muscles involved are the sternomastoids and facial muscles, but the muscles of mastication may also become involved, with progress to other muscle groups. Myotonic features are seen early and followed by muscle wasting. Other features are premature baldness, cataracts, testicular atrophy and cardiomyopathy.

Myasthenia gravis. An autoimmune disorder with defective neuromuscular transmission, which may first present as weakness of ocular movement or even facial movement.

Myelodysplastic syndrome. A spectrum of essentially preleukaemic states.

Myeloma. A plasma cell tumour. Typically progresses to myelomatosis, but can present as:

- soft-tissue myeloma
- solitary osseous myeloma
- multiple myeloma (myelomatosis) – a disease mainly of middle-aged and older people, and sometimes related to exposure to ionizing radiation or petroleum products. The initial feature is abnormal serum immunoglobulins, occasionally detectable by chance, raised ESR, rouleaux formation or high plasma viscosity, or serum protein investigations. Years may elapse before discrete, punched-out radiolucent osteolytic lesions appear, especially in the skull and jaws. When the jaws are involved there may be pain, paraesthesia or anaesthesia, loosening of teeth and pathological fracture. Anaemia, weakness and weight loss are manifestations of advanced disease. A few patients also develop amyloidosis. Neoplastic proliferation of plasma cells in the bone marrow and their release of cytokines, such as interleukin-1, ultimately causes hypercalcaemia, renal failure, suppression of haemopoiesis and many other secondary effects. The abnormal

immunoglobulins have defective antibody activity, and thus infections occur, and there may be plasma hyperviscosity with a clotting or bleeding tendency and neurological sequelae.

Diagnosis depends on showing:

- a monoclonal immunoglobulin peak on serum electrophoresis
- spillover of light chains into the urine (Bence-Jones proteinuria)
- plasma cell neoplasia on marrow biopsy
- osteolytic lesions on skeletal radiographs or by bone scanning.

Management is by radiotherapy and cytotoxic chemotherapy.

Myositis ossificans. A rare idiopathic condition in which muscles ossify. Occasionally the same reaction follows trauma to muscle. Radiographs tend to show the calcifications and alkaline phosphatase levels are markedly raised.

Myxoma. Rare in the oral cavity, this can arise in bone or soft tissue and, although benign, is aggressive and difficult to eradicate because it tends to infiltrate normal tissue.

Necrotizing sialometaplasia. A rare condition in which there is ulceration, usually in a smoker in the palate, which heals spontaneously over several weeks. Associated with salivary gland infarction, histology can be confusing, since it has an appearance resembling neoplasia (pseudoepitheliomatous hyperplasia).

Nerve sheath tumours. Neoplasms arising from a nerve or showing nerve sheath differentiation. Benign and malignant (MNST) variants. Several distinct benign subtypes are recognized, including Schwannoma (neurilemoma, neurinoma), neurofibroma and perineurioma:

- *Schwannomas* – (see below)
- *Neurofibromas* – unencapsulated tumours composed of spindle cells in a fibromyxoid stroma
- *Perineuriomas* – arise in soft tissues or nerves, and are composed of cells with elongated bipolar cytoplasmic processes arranged in whorls or a storiform pattern. The neoplastic cells express vimentin and epithelial membrane antigen, but are negative for S-100 protein, desmin, muscle-specific actin, and CD34.

Most malignant NSTs arise from Schwann cells, and approximately two-thirds are associated with neurofibromas.

Neurilemmoma (Schwannoma). A rare benign encapsulated neoplasm of neurilemmal cells of the nerve axonal sheath with distinct Antoni A and B components, hyaline vessel walls, and nuclear palisading. Tumour

cells are strongly immunopositive for S-100 protein. Presents as a slowly enlarging painless mass, usually in the tongue, sometimes with facial pain and/or atrophy of the muscles of mastication. Facial nerve Schwannomas can cause facial palsy or compressive hearing loss resulting from ossicular interference and sensorineural hearing loss due to effects on cochlear nerve in the internal auditory canal. Can present with vestibular symptoms resulting from compression of the vestibular nerve; sensorineural hearing loss, tinnitus and disequilibrium. Schwannomas that arise from the glossopharyngeal, vagus or accessory nerves can be in the jugular foramen and present with variable cerebellar and acoustic symptoms, or can cause glossopharyngeal dysfunction (e.g. hoarseness, difficulty swallowing) and/or spinal accessory symptoms (e.g. trapezius atrophy). Schwannomas involving the oculomotor, trochlear and abducens nerves are rare, but can include palsy of the affected muscle and ipsilateral cavernous sinus symptoms if the mass is in the sinus. Hypoglossal Schwannomas can present with ipsilateral deviation of the tongue, possibly with associated hemiatrophy.

Neurofibromas. (See Von Recklinghausen's disease.) Neurofibromas occasionally undergo sarcomatous change. Mucosal 'neurofibromas' (plexiform neuroomas) may be seen in multiple endocrine neoplasia type III syndrome (with medullary carcinoma of the thyroid). Management is by excision. Neurofibromatosis type 2 (NF2) is also called the multiple inherited Schwannomas, meningiomas and ependymomas (MISME) syndrome. Diagnosis is by biopsy.

Noma (cancrum oris; gangrenous stomatitis). Gangrene that may follow acute ulcerative gingivitis in malnourished, debilitated, or severely immunocompromised patients. Anaerobes, particularly *Bacteroides* (*Porphyromonas*) species, *Fusobacterium necrophorum* (an animal pathogen), *Prevotella intermedia*, *Actinomyces* and alpha haemolytic streptococci, have been implicated. In cases flowing ANUG, *Streptococcus anginosus* and *Abiotrophia* spp. are the predominant species. In early noma, predominant species include *Ochrobactrum anthropi*, *Stenotrophomonas maltophilia*, an uncharacterized species of *Dialister*, and an uncultivated phylotype of *Leptotrichia*. A range of species or phylotypes are found in advanced noma, including *Propionibacterium acnes*, *Staphylococcus* spp., *Stenotrophomonas maltophilia*, *Ochrobactrum anthropi*, *Achromobacter* spp., *Afipia* spp., *Brevundimonas diminuta*, *Capnocytophaga* spp., *Cardiobacterium* spp., *Eikenella corrodens*, *Fusobacterium* spp., *Gemella haemophylans*, and *Neisseria* spp. Phylotypes unique to noma infections include those in the genera *Eubacterium*, *Flavobacterium*, *Kocuria*, *Microbacterium*, and *Porphyromonas* and the related *Streptococcus salivarius* and genera *Sphingomonas* and *Treponema*. Spreading necrosis penetrates the buccal mucosa, leading to

gangrene and an orocutaneous fistula and scarring. Diagnosis is clinical; an immune defect should always be excluded. Management includes improving nutrition, systemic antibiotics (clindamycin, penicillin, tetracyclines or metronidazole) and plastic surgery.

Orofacial-digital syndromes. A group of inherited conditions manifesting with cleft lip and other facial anomalies, tongue clefts and multiple fraenae. Various dental defects, lingual and gingival nodules may be seen.

Orofacial granulomatosis (OFG). An uncommon condition seen mainly in adolescents and young adults which can manifest with facial and/or labial swelling, angular stomatitis and/or cracked lips, ulcers, mucosal tags, cobblestoning or gingival hyperplasia. The aetiology is unknown, but some have or develop, gastrointestinal Crohn's or sarcoidosis; others have a postulated reaction to food or other antigens (e.g. benzoates or cinnamon), metals, such as cobalt, or paratuberculosis or mycobacterial stress protein mSP65. Diagnosis is clinical, supported by blood tests, radiology, endoscopy, and biopsy to differentiate from sarcoid, Crohn's disease, tuberculosis and foreign body reactions. Management is to eliminate allergens and treat lesions with intralesional corticosteroids or, occasionally, systemic clofazimine or sulfasalazine.

Ossifying fibroma. This has features both of a developmental anomaly and a neoplasm. It presents as a painless, localized slow-growing, hard swelling of the jaw which radiographically is a well-defined radiolucency with a thin sclerotic margin containing irregular opaque masses. Histological examination shows little or no distinction between ossifying fibroma and fibrous dysplasia, except perhaps that a cellular, homogeneous calcified material is usually more obvious in ossifying fibroma. Distinction between ossifying fibroma and fibrous dysplasia, therefore, relies heavily on the localized nature and slow growth pattern of the ossifying fibroma. Surgical enucleation is curative.

Osteitis deformans. Paget's disease.

Osteochondroma (osteocartilaginous exostosis). Arises from the epiphyseal region of bone as cartilage-capped bony outgrowths, usually in children. Lesions may be solitary, or multiple in the syndrome of hereditary multiple exostoses. In the jaws the most common site is the coronoid process. Solitary lesions are entirely benign, but in patients with multiple osteochondromas there is a significant risk of malignant change.

Osteogenesis imperfecta (brittle bone syndrome; fragilitas ossium). A group of at least four types of inherited bone disorder characterized by excessive bone fragility and a number of extraskeletal connective tissue disorders. Affected children may have multiple rib fractures (giving a 'beaded' radiographic appearance) and shortened concertina-like

long bones. The skull is soft, with multiple wormian bones. Fracture of limb bones following mild injury is the most common skeletal problem. Patients are usually of short stature, with grossly deformed limbs and deformities of the spine and trunk and often cannot walk. Some have dentinogenesis imperfecta.

Blue sclera occur in up to 90% of all patients. Deafness is common due to defective sound conduction through the external and middle ear. Hormones (calcitonin), vitamins (e.g. vitamin C or D), fluoride and flavonoids are of little value and surgical intervention for skeletal deformities is usually needed.

Osteoid osteoma and osteoblastoma. Benign bone tumours that are uncommon in the skeleton generally and rare in the jaws. The microscopic features of these tumours are similar, but they have distinctive clinical and radiological features. Osteoid osteoma is usually seen in adolescents and young adults, most frequently in the femur and tibia, is often painful (particularly at night) and has a characteristic central radiolucent area or nidus surrounded by a rim of densely sclerotic bone of variable thickness. Osteoblastoma, on the other hand, shows progressive growth without the osteosclerotic rim and is rarely painful. Microscopically both lesions consist of a vascular stroma in which there are trabeculae of osteoid surrounded by numerous, and darkly staining, osteoblasts.

Osteoma. A benign bone neoplasm which grows by the continuous formation of lamellar bone; it should be distinguished from an exostosis. Osteomas are usually unilateral, painless, hard smooth swellings covered by normal oral mucosa. Multiple osteomas and polyposis coli are features of Gardner syndrome; the polyps in the large bowel may become malignant.

Osteomyelitis. This literally means 'inflammation of the bone marrow', although sometimes the subperiosteal bone is mainly affected. Acute osteomyelitis primarily affects the mandible, usually affects adults and is essentially an osteolytic, destructive process, but an osteoblastic response is typical of sclerosing osteomyelitis. In children, proliferative periostitis may occur. Bacteria can spread to bone:

- from local odontogenic infections (the commonest cause)
- from other adjacent structures (e.g. otitis media, tonsillitis, suppurative sialadenitis)
- haematogenous spread of organisms (this is rare in relation to the jaws).-

When osteomyelitis of the mandible does occur, it may be a sign of an underlying debilitating disease, such as diabetes mellitus, an immune defect, or the effects of alcoholism: alternatively, it may be related to reduced vascularity, such as after irradiation or in

rare conditions like Paget's disease or osteopetrosis. *Staphylococcus aureus* is the commonest organism causing osteomyelitis in the jaws, but streptococci (both α - and β -haemolytic) and anaerobic organisms (e.g. *Bacteroides* and *Peptostreptococci* species) are occasionally implicated.

In acute osteomyelitis the organisms excite acute inflammation in the medullary bone and the consequent oedema and exudation causes pus to be forced under pressure through the medullary bone. The pressure causes thrombosis of intrabony vessels (i.e. the inferior dental artery), reducing the vascular supply to the bone, which then necroses. Eventually pus bursts through the cortical plate to drain via sinuses in the skin or mucosa. Where pus penetrates the cortex it may spread subperiosteally, stripping the periosteum and, thus, further reducing the blood supply. Necrotic bone becomes sequestrae surrounded by pus and these either spontaneously discharge or remain and perpetuate infection. The periosteum lays down new bone to form an involucrum encasing the infected and sequestered bone. The involucrum, although perforated by sinuses, may prevent sequestra from being shed. Finally, if little new bone is formed, a pathological fracture may occur. Mandibular osteomyelitis presents with a deep-seated, boring pain and swelling. Teeth in the affected segment are mobile and tender to percussion, and pus oozes from the gingival crevices. Once pus penetrates the cortical plate the pain improves and discharge appears. Labial anaesthesia is a characteristic feature because of pressure on the inferior alveolar nerve. The patient is often febrile and toxic with enlarged regional lymph nodes. Diagnosis is clinical, supported by imaging which, in established cases, shows marked bony destruction and sequestration but, since the changes are seen only after there has been significant decalcification of bone, early cases may not be detected and, in these, isotope bone scanning using technetium diphosphonate may show increased uptake. There is a leucocytosis with neutrophilia, and a raised erythrocyte sedimentation rate. Treatment is by antibiotic therapy and usually drainage. Penicillin is the drug of choice, but many staphylococci are now penicillin-resistant, and for these infections, flucloxacillin or fusidic acid may be used. Lincomycin and clindamycin also give high bone levels, but, because of a high incidence of pseudo-membranous colitis, are now regarded as second-line drugs. Metronidazole gives good bone levels and is indicated where anaerobic infection is suspected. Drainage of established pus follows the same guidelines used for other infections. When dead bone is exposed in the mouth, it can often be left to sequestrate without surgical interference, but sequestrectomy should be undertaken if the separated dead bone fails to discharge and decortication of the

mandible may be needed in order to allow this and drainage.

Hyperbaric oxygen is an effective adjunct for recalcitrant osteomyelitis, especially where anaerobic organisms are involved:

- *Acute maxillary osteomyelitis* This is seen rarely, and usually in infants, presumably because the lack of development of the antrum at this age makes the maxilla a dense bone.
- *Chronic osteomyelitis* This presents with intermittent pain and swelling, relieved by the discharge of pus through longstanding sinuses. Bone destruction is localized and often a single sequestrum may be the source of chronic infection. Removal of the sequestrum and curettage of the associated granulation tissue usually produces complete resolution.
- *Focal sclerosing osteomyelitis* This is usually asymptomatic and is revealed as an incidental radiographic finding. Most common in young adults, it is usually associated with apical infection of a mandibular molar. Radiographically there is a dense, radio-opaque area of sclerotic bone related to the tooth apical area, caused by formation of endosteal bone. This appears to be a response to low-grade infection in a highly immune host. Following tooth extraction the infection usually resolves (but the area of sclerotic bone often remains).
- *Diffuse sclerosing osteomyelitis* A sclerotic endosteal reaction that, like focal sclerosing osteomyelitis, appears to be a response to low-grade infection. However, the area of bone involved is widespread and it sometimes involves most of the mandible or occasionally the maxilla. Sometimes the infection arises in an abnormally osteosclerotic mandible, such as in Paget's disease, osteopetrosis or fibrous dysplasia. Intermittent swelling, pain and discharge of pus may persist for years. Management is difficult because of the extensive nature of the disease process. Long-term antibiotics, curettage and limited sequestrectomy all have their place.
- *Proliferative periostitis (Garré's osteomyelitis)* This is more common in children than adults. The cellular osteogenic periosteum of the child responds to low-grade infection, such as apical infection of a lower first molar tooth, by proliferation and deposition of subperiosteal new bone. The subperiosteal bone may be deposited in layers, producing an onion-skin appearance radiologically, which can simulate Ewing sarcoma. The endosteal bone, however, may appear to be completely normal, but in severe cases also appears moth-eaten radiologically. Removal of the infective source is usually followed by complete resolution, although

subsequent bone remodelling can take a considerable time.

Osteonecrosis of jaws (ONJ). ONJ, or osteochemonecrosis, can arise in people who have used bisphosphonates. Intravenous bisphosphonates, such as Pamidronate (Aredia) and Zoledronate (Zometa), are a particular high risk, but even oral bisphosphonates used for more than 3 years are a risk. ONJ usually presents after dental treatment, especially surgery, with painful, exposed and necrotic bone, primarily of the alveolar bone of the mandible. Therefore, it is best to avoid elective oral surgery, including endosseous implant placement, or the treatment should be carried out well before commencing bisphosphonates. Therapy is primarily supportive, involving nutritional support along with superficial debridement and oral saline irrigation. Antibiotics are indicated only for definite secondary infection. Dead necrotic bone requires resection. Vascularized free tissue transfer provides an immediate reconstruction option with a shortened treatment course.

Osteoradionecrosis (ORN). This can arise in people who have been irradiated in the region of the jaws. It presents similarly to ONJ. It can be spontaneous, but it most commonly results from tissue injury, especially surgery. Therapy is as for ONJ, plus hyperbaric oxygen.

Osteopetrosis (marble bone disease; Albers-Schönberg disease). Bone disease characterized by increased bone density with replacement of normal medullary bone by irregular avascular bone. Marrow is replaced by bone, and thus extramedullary sites such as the liver, spleen and lymph nodes develop haemopoietic function. Osteopetrosis is inherited in an autosomal-dominant or recessive manner. Patients with the autosomal-dominant form of osteopetrosis have good general health and a normal lifespan. There is no effective treatment for the recessive form: regular blood transfusions, steroids and splenectomy may correct the anaemia; cranial nerve decompression may be necessary and, if hydrocephalus develops, ventricular shunts may be required. However, most affected children die in the first decade of life, usually as a consequence of overwhelming infection or haemorrhage. The jaws, particularly the maxillae, are thickened and sclerotic and the paranasal sinuses are often reduced in size. Recurrent sinusitis and cranial nerve palsies (especially II, III, V, VII and VIII) are other orofacial problems of osteopetrosis. Children with the recessive form of osteopetrosis may have teeth with hypoplastic enamel, shortened roots and an increased susceptibility to caries. Eruption of teeth can be delayed or absent. Pathological fracture is common. As a consequence of the sclerotic bone, dental extractions can be difficult and the mandible also liable to fracture. The reduced vascularity of bone predisposes to postextraction osteomyelitis.

Osteoporosis. A fairly common condition, characterized by the loss of both the organic matrix and the mineralized components of bone, although serum biochemistry is normal. The most common cause of osteoporosis is ageing, especially in females (hormonal), but drugs (especially corticosteroids) and several other disorders can also increase the rate of bone loss. The main clinical problem of osteoporosis is fracture of either the neck of femur or collapse of vertebral bodies. Osteoporosis has no notable oral manifestations, but may affect the jaws and predispose to fracture or periodontal bone loss. Osteoporosis is managed by treatment of the underlying disorder (where possible) and by use of stimulators of osteogenesis (fluoride, phosphate, sex hormones or parathyroid hormone) or inhibitors of bone resorption (e.g. calcium, vitamin D, bisphosphonates). The bisphosphonates predispose to osteonecrosis of the jaws.

Osteosarcoma. An aggressive malignant neoplasm which typically affects young patients. Males are affected twice as frequently as females. Only rarely are the mandible or maxilla affected. The aetiology is largely unknown, although about 3% of patients with osteosarcomas have a history of irradiation for other lesions. It should be noted that there is another peak incidence of osteosarcoma in the over-50s, which probably represents the small but significant malignant change in patients with pre-existing Paget's disease. Osteosarcomas are classified as either sclerosing or osteolytic, depending on the degree of bone formation or destruction, and may be predominantly medullary or subperiosteal. A rare subtype called a *parosteal or juxtacortical osteosarcoma*, grows from the superficial surface of the bone and is relatively well differentiated. This variant grows much more slowly than the conventional osteosarcoma and metastasizes late. A characteristic feature of osteosarcoma is the 'sunray' appearance on radiography. In the jaws, symmetrical widening of the periodontal ligament in associated teeth may be an early sign. Although the prognosis for osteosarcomas of the jaws is marginally better than for those of the long bones, the outlook is usually poor.

Pachyderma oralis. White sponge naevus.

Pachyonychia congenita. A rare, usually autosomal-dominant syndrome, in which the main clinical sign is onychodystrophy of all finger and toe nails. There may be oral white lesions.

Papillomas. The most common benign soft tissue neoplasms; usually caused by human papilloma virus (HPV) infections. Commonly asymptomatic, a papilloma is a pedunculated lesion, either pink or white if hyperkeratinized, on the palate, tongue or other sites. Diagnosis is confirmed by biopsy (Fig. 44.12). Management is with topical podophyllin or intralesional α -interferon, imiquimod or surgery.

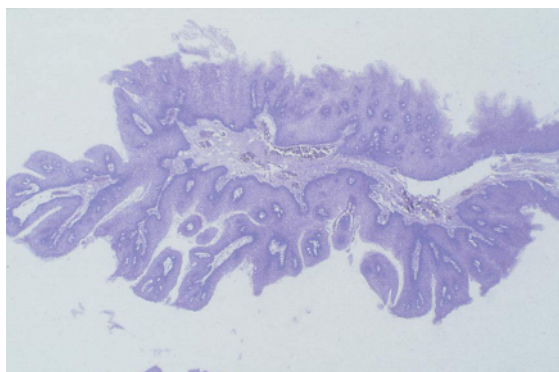


Fig. 44.12 Papilloma

Paraneoplastic pemphigus. This is associated mainly with non-Hodgkin's lymphoma, chronic lymphoid leukaemia, sarcomas, thymomas or Castleman's disease. There are serum autoantibodies reacting with transitional epithelium, and lichenoid features on biopsy, with intra- and subepithelial clefting, and IgG and C3 deposits. Antibodies are directed against desmosomes and hemidesmosomes, especially against desmoplakin or BP1. Clinical features include severe stomatitis and cheilitis in all cases, conjunctival lesions, genital lesions, and polymorphous skin eruption on the trunk, palms and soles.

Periodic fever, aphthae, pharyngitis and adenopathy (PFAPA). An unusual cause of mouth ulceration (with the other features) in children, which appears to respond to cimetidine. Aetiology is unclear.

Phakomatoses. The term given to a range of disorders affecting ectoderm, with neurological manifestations and sometimes with learning disability, which include: Sturge-Weber syndrome, Von Recklinghausen's neurofibromatosis, ataxia telangiectasia and tuberous sclerosis (epiloia; Bourneville disease).

Pharyngeal pouch. A rare pulsion diverticulum that appears because of a potential weakness in the pharyngeal muscles. Dysphagia characterized by regurgitation of food results and may cause aspiration into the lungs.

Porphyrias A group of rare disorders of porphyrin metabolism:

- *Erythropoietic porphyria* may cause reddish discolouration of both dentitions, hirsutism, and skin blisters.
- *Hepatic porphyria* predisposes to mouth blisters (and is a contraindication to use of intravenous barbiturates).

Pregnancy gingivitis. An exacerbation of chronic gingivitis by pregnancy. Common mainly after the second month of pregnancy, pregnancy gingivitis presents with erythema, swelling and liability to bleed. Occasionally, a proliferative response at the

site of a particularly dense plaque accumulation leads to a pregnancy epulis (pyogenic granuloma). This is a soft, red or occasionally firm swelling of the dental papilla. It may be asymptomatic unless traumatized by biting or toothbrushing. Oral hygiene should be improved. If asymptomatic, an epulis should be left alone – it may regress after parturition. If symptomatic, excision biopsy is indicated.

Progeria (werner syndrome). A collagen abnormality causing dwarfism, premature ageing and a characteristic facial appearance due to a disproportionately small face with mandibular retrognathia and a beak-like nose. Death occurs usually in the mid-teens.

Pseudoxanthoma elasticum. An autosomal-recessive condition of progressive calcification of elastic tissue in the retina, skin, cardiovascular system, and oral lesions of yellow plaques, somewhat resembling Fordyce spots.

Psoriasis. Psoriasis of the oral mucosa is rare and is characterized by erythema, white or greyish plaques, and lesions similar to erythema migrans. Gingival involvement in the form of desquamative gingivitis may rarely be seen. Biopsy, with histological and immunostaining are essential to the diagnosis. Topical corticosteroids may be helpful in these cases.

Purpura. The red or brown pinpoint lesions (petechiae) or diffuse bruising (ecchymoses) mainly at sites of trauma, especially in persons with blood platelet disorders or where there is trauma, such as in fellatio or vomiting in bulimia. Lesions do not blanch on pressure (cf. haemangioma). Occasional small traumatic petechiae are seen at the occlusal line in otherwise healthy patients. Platelet deficiency is usually idiopathic (autoimmune), sometimes in infectious mononucleosis, HIV disease, rubella or renal disease. Localized oral purpura may appear for no apparent reason ('angina bullosa haemorrhagica'). Diagnosis is from a blood picture and haemostatic function to differentiate from haemangiomas, telangiectasia and Kaposi sarcoma. Treatment is of the underlying cause.

Pyogenic granuloma. A possibly reactive vascular lesion, sometimes associated with pregnancy. Typically, a pyogenic granuloma is a small (<3cm) red painless mass that bleeds easily, ulcerates and grows rapidly and is frequently seen on the gingival margin or tongue (Fig. 44.13). Treatment is excision to exclude angiomatous proliferations, chancre, carcinoma or Kaposi sarcoma.

Pyostomatitis vegetans. Oral condition characterized by milium pustules and ulcers or erosions affecting the gingivae, particularly labially, and the buccal, labial, lingual or palatal mucosae, typically associated with, and following the onset of, inflammatory bowel disease. Biopsy of perilesional tissue, with histological and immunostaining examination are essential to



Fig. 44.13 Pyogenic granuloma

the diagnosis. The oral lesions may respond at least partially to topical corticosteroids. The underlying disease should be treated, typically with dapsone, systemic corticosteroids, sulphasalazine, azathioprine or sulphamethoxypyridazine. Some patients report benefit from zinc supplementation. Lesions may resolve following colectomy.

Radiolucencies. Radiolucent lesions in the jaws may be due to cysts, infection, neoplasms arising in bone and metastatic neoplasms, bone disease (hyperparathyroidism, hypophosphatasia, cherubism; fibrous dysplasia; osteoporosis; osteonecrosis) and bone marrow expansion (haemolytic anaemias) or odontogenic cysts or tumours.

Radio-opacities. Radio-opaque lesions in the jaws may be due to unexpected teeth, foreign bodies, bone disease (osteomyelitis; fibrous dysplasia; Paget's disease; Gardner's syndrome; osteopetrosis; neoplasms arising in bone and metastatic neoplasms especially from the prostate) or odontogenic lesions such as odontomes, hypercementosis, and calcifying odontogenic tumour.

Rickets and osteomalacia. Bone diseases characterized by a decrease in the mineral, but not organic, content of bone. Unmineralized osteoid is present in large amounts, but there is a deficiency of mature mineralized bone. The term 'rickets' is used when the disorder affects children (when bones are still growing), the term 'osteomalacia' when adults are affected. The most common cause of rickets and osteomalacia in the western world is a deficiency of vitamin D, which can arise from dietary deficiency of vitamin D, gastrointestinal disease or in disorders of vitamin D metabolism. Dietary deficiency of vitamin D is still seen in elderly reclusive patients and in Asians living in Northern Europe on a poor diet which also contains phytates (such as in chapatis), since these inhibit calcium absorption from the gut, especially if they have little sun exposure in purdah. Vitamin D is normally synthesized in skin stimulated by sunlight. Renal disease

impairs the conversion of vitamin D to dihydroxycholecalciferol and consequently can lead to 'renal rickets'. Rickets is clinically characterized by a spectrum of bony deformities, which range from mild bowing of the long bones of the legs to gross skeletal deformity and dwarfism. Osteomalacia causes generalized bone pain and tenderness, vertebral collapse, pelvic deformities and myopathy. Correction of any underlying clinical disorder is required and supplements of one of the metabolites of cholecalciferol are the usual lines of therapy for osteomalacia and rickets.

Rubella. A highly infectious viral disease that causes cervical lymphadenopathy, a macular rash starting on the face and behind the ears, mild fever, sore throat and, occasionally, palatal petechiae. Transplacental infection of the fetus may cause high-tone deafness, learning disability, blindness, cardiac defects or death.

Salivary fistula. An abnormal communication between the gland or ducts and skin or mucous membrane. Internal fistulae are uncommon and asymptomatic. Trauma to the major glands or duct may (rarely) cause a persistent external fistula that is unpleasant and may lead to infection. Surgical repair is then indicated.

Salivary duct obstruction (obstructive sialadenitis). Not uncommon and usually caused by:

- a calculus (stone)
- rarely oedema from irritation of the duct by, for example, a denture clasp
- 'physiological' duct obstruction due either to duct spasm or an abnormal passage of the parotid duct through the buccinator or in relation to the masseter muscles
- mucus plug
- neoplasm
- stricture.

Duct obstruction can cause salivary gland swelling and pain. Prolonged duct obstruction produces atrophy, particularly of serous acini, such as in the parotid gland:

- Most obstructions are calculi in the submandibular duct or mucous plugs in the parotid.
- A history of painful salivary gland swelling just before, or at, mealtimes is classical of obstruction.
- In older patients, there may be only dull pain over the affected gland, referred elsewhere.
- It is occasionally possible clinically to determine the cause of major duct obstruction if a calculus is palpable or visible.
- In other cases, radiographs may reveal a calculus if radio-opaque. Two views at 90° are required.
- Sialography should help differentiate the various causes of major duct obstruction: intraductal or ductal causes are usually readily seen, but 'physiological' obstructions require pressure-monitored sialographic techniques for detection.

- Extraductal obstruction may be clinically obvious or apparent only on sialography or combined CT sialography.
- CT, MRI or ultrasonography are occasionally required.

Intraductal and ductal causes of duct obstruction are usually correctable by the removal of the cause (e.g. calculus or mucus plug) or, in a benign stricture, by repeated duct dilatation with a lacrimal duct dilator.

Sarcoidosis. An uncommon chronic granulomatous reaction, of unknown aetiology, prevalent particularly in black females. It presents with cervical lymphadenopathy, enlarged salivary glands and xerostomia. Heerfordt syndrome (salivary and lacrimal swelling, facial palsy and uveitis), mucosal nodules, gingival hyperplasia or labial swelling are rare. Oral lesions may occasionally precede systemic involvement. Biopsy of minor salivary glands reveals granulomas in up to 20%, particularly in patients with hilar lymphadenopathy. Diagnosis is by biopsy, chest radiography, gallium scan, raised serum angiotensin converting enzyme and adenosine deaminase, to differentiate from Crohn's disease, tuberculosis and foreign body reactions. Management is with intralesional corticosteroids; systemic steroids if the lung or eye are involved.

Scleroderma. An uncommon idiopathic connective tissue disease seen mainly in middle-aged females. Clinical features include oral telangiectases, restricted mouth opening with microstomia, pale fibrotic 'chicken' tongue and a widened periodontal space on radiography, but the teeth are not mobile. The CREST syndrome (calcinosis, Raynaud syndrome, oesophageal lesions, sclerodactyly, telangiectasia) is a rare variant. Diagnosis is from clinical features, histopathology and auto-antibodies (ANA and Scl 70 especially). Management is often with penicillamine.

Scurvy - vitamin C (ascorbic acid) deficiency. Arises when no fresh fruit or vegetables are eaten for a long period. Diffusely swollen, boggy, and purplish gingivae with purpura and haemorrhage are seen. Diagnosis is from leukaemia mainly from the dietary history, clinical features, blood film and white cell ascorbic acid. Management is with vitamin C.

Sialadenitis. The organisms most commonly isolated from bacterial ascending sialadenitis are α -haemolytic streptococci, such as *Streptococcus viridans* and *Staphylococcus aureus*, the latter frequently being penicillin-resistant. Reduced salivary flow allows retrograde access of bacteria from the oral cavity, associated with:

- dehydration, such as following gastrointestinal surgery
- radiotherapy for oral or salivary tumours
- gland or duct abnormalities or obstruction
- Sjögren syndrome.

Acute parotitis presents with:

- painful swollen salivary gland
- the overlying skin may be reddened
- pus may exude from the parotid duct
- if the infection localizes as a parotid abscess it may point externally through the overlying skin or, rarely, into the external acoustic meatus
- trismus
- pyrexia
- cervical lymphadenopathy
- leucocytosis.

Diagnosis is on clinical grounds. Investigations may be needed to exclude hyposalivation. Management is as follows:

- Collect pus for a stained smear, culture and antibiotic sensitivity testing.
- Body temperature should be noted.
- Cervical lymphadenopathy should be excluded.
- Antibiotic therapy should be commenced orally. The antibiotic of choice is flucloxacillin, with erythromycin as an alternative if the patient is penicillin allergic.
- Any fluctuant swelling should be surgically drained.
- Supportive therapy, such as ensuring an adequate fluid intake, analgesics and attention to good oral hygiene, is important.

Once the acute condition has resolved, sialography should be undertaken to identify correctable factors, such as mucus plugs, strictures or calculi.

- Chronic bacterial sialadenitis. This may develop following acute sialadenitis, particularly if treatment is inadequate, or predisposing factors are not eliminated. Unfortunately, serous acini may atrophy when salivary outflow is chronically obstructed and this further reduces salivary function.

Sialadenosis. An uncommon, benign non-inflammatory, non-neoplastic bilaterally symmetrical and painless enlargement of salivary glands. A variety of causes of sialadenosis (sialosis) are recognized, most associated with autonomic neuropathy, including:

- *drugs:*
 - alcohol abuse with or without accompanying liver cirrhosis
 - sympathomimetic agents such as isoprenaline
 - phenylbutazone, isoprenaline, antithyroid drugs and phenothiazines.
- *endocrine conditions:*
 - diabetes mellitus
 - pregnancy
 - acromegaly
 - following oophorectomy.

- *nutritional disorders:*

- malnutrition
- anorexia nervosa
- bulimia
- cystic fibrosis and pancreatitis.

Sialadenosis usually affects both parotids. Clinically there is soft, painless general enlargement of the involved glands. A useful guide to whether the patient is simply obese or has parotid enlargement is to observe the outward deflection of the ear lobe, which is seen in true parotid swelling. The diagnosis of sialadenosis is one of exclusion, based mainly on history and clinical examination. Investigations indicated may include the following:

- Blood tests: for raised glucose levels or abnormal liver function.
- Sialography: reveals enlarged but otherwise normal glands, although salivary secretion is not impaired. However, if a bilateral space-occupying lesion, such as a salivary neoplasm, cyst or lymphoid neoplasm presents difficulties in differentiation, sialography or MRI may help.
- Ultrasound: rarely, a bilateral space-occupying lesion such as a salivary neoplasm, cyst or lymphoid neoplasm may present difficulties in differentiation from sialadenosis, and then ultrasound may help.
- Biopsy is rarely needed. The affected glands show acinar hypertrophy, which appears related to an autonomic neuropathy.
- Sialochemistry shows raised potassium and calcium levels, which are not found in other causes of parotid enlargement.

No treatment is available. If investigations have revealed a likely cause such as alcoholism or diabetes, then sialadenosis may resolve when alcohol intake is reduced or glucose control is instituted.

Solitary bone cysts. Lesions that occur most commonly in the long bones, they may also be found occasionally in the jaws. Their cause is speculative, but they may arise after trauma to the bone when an intramedullary haematoma forms and then degenerates rather than healing. Haemorrhagic bone cysts are generally painless and expansion is uncommon, the lesions usually being coincidentally discovered during radiographic examination. They are seen most often in the posterior body of the mandible in young persons. Clear or blood-stained fluid may be found within the bony cavity, but preoperative aspiration may at times not yield any product. Radiologically there is a well-defined translucency with a scalloped appearance around the apices of the teeth, which are vital. Surgery is undertaken in order to make a definitive diagnosis. There is no detectable cyst lining and sometimes only a thin fibrous membrane. Curettage produces bone fragments

and connective tissue sometimes with granulation tissue. However, such surgical opening of the cavity usually leads to spontaneous resolution.

Subepithelial immune blistering diseases. These include pemphigoid variants, dermatitis herpetiformis, acquired epidermolysis bullosa, linear IgA disease and chronic bullous disease of childhood.

Submucous fibrosis [oral submucous fibrosis (OSMF)].

Virtually only a disease of adults from Asia, related to the use of areca nuts, now also found in Pan Masala and Gutkha. It is possible that it is due to the copper content which increases collagen cross-linking. Tight vertical bands in the buccal mucosa may progress to severely restricted oral opening. OSMF can also affect the soft palate or tongue. It produces epithelial atrophy, and there is a malignant potential – carcinoma develops possibly in up to 8%. It is usually easily diagnosed, since it is extremely rare in people not of Asian extraction. There is a history of betel chewing and no history of other injury or surgery. Diagnosis is from the clinical features, biopsy and haematology. Often anaemia is present. Management is to stop use of areca nut. Asymptomatic cases should be observed only. Symptomatic cases with restricted opening may respond to exercises, intralesional corticosteroids, penicillamine, interferon or surgery (usually excision of the ‘scarred’ tissue in the cheeks and transposition of bilateral palatal island flaps).

Superior vena cava obstruction. Obstruction of cardiac venous return, usually by lung cancer, may produce oedema and cyanosis of face, neck and arms.

Surgical emphysema. Escape of air into the tissues, usually after using an air rotor to section a tooth for removal, may give rise to diffuse swelling, which characteristically is painless, but gives rise to crepitus on palpation.

Syphilis. A sexually transmitted infection caused by *Treponema pallidum*. Other treponematoses, including yaws, bejel and pinta, are rare in the developed world:

- **Congenital syphilis** This manifests with frontal bossing, saddle nose, Hutchinsonian incisors, Moon’s or mulberry molars and rhagades. Learning disability, interstitial keratitis, deafness, sabre tibiae and Clutton’s joints may be seen.
- **Acquired syphilis** Predominantly an infection of the sexually promiscuous (prostitutes, men who have sex with men, travellers, armed forces). Diagnosis is by direct smear of primary and secondary stage lesions. Serology becomes positive late in the primary stage. Penicillin by injection (or erythromycin or tetracycline). Incubation period 9–90 days.
- **Primary syphilis (Hunterian or hard chancre)** This is a small papule which develops into a large painless indurated ulcer, with regional lymphadenitis. A chancre heals spontaneously in 1–2 months. Rare on the lip (upper) or intraorally – usually the tongue.

Treponema pallidum in smear (dark-field examination). Serology is positive late in this stage. Differentiate from trauma, herpes labialis, pyogenic granuloma and carcinoma.

- **Secondary syphilis** oral lesions include mucous patches, split papules or snail-track ulcers, which are highly infectious. Rash (coppery coloured typically on palms and soles), condylomata lata and generalized lymph node enlargement can also be present.
- **Tertiary syphilis** This may cause glossitis (leukoplakia) and gumma (usually midline in the palate or tongue). These are non-infectious, but may be associated with cardiovascular complications (aortic aneurysm) or neurosyphilis (tabes dorsalis, general paralysis of the insane, Argyll–Robinson pupils).

Thyroglossal cyst. Arises from remnants of the thyroglossal duct and is midline at any point between the tongue and thyroid gland, and moves up on protrusion of the tongue. The cyst may cause dysphagia or become infected. It should be surgically removed.

Tooth root resorption. Can arise because of:

- chronic infection
- chronic trauma
- impactions
- cysts and tumours
- tooth subluxation, luxation or radiotherapy
- systemic disease (Paget’s disease; hypo or hyperparathyroidism; Turner’s syndrome; Gaucher’s disease or calcinosis).

Tooth surface loss. Tooth surface loss includes attrition (Fig. 44.14), abrasion and erosion (and possibly abfraction).

Torus palatinus and mandibularis. Developmental benign exostoses with a smooth or nodular surface, tori are common conditions of no consequence apart from occasionally interfering with denture construction. Torus palatinus occurs in the centre of the hard palate, is of variable size and may have a smooth or nodular surface (Fig. 44.15). The torus is more common in Mongoloid races and may become more apparent with increasing age. Torus mandibularis is lingual to the lower premolars and usually bilateral. Although there is no association with torus palatinus, the torus mandibularis is also seen most commonly in mongoloids and is more apparent with increasing age. Mandibular tori are usually located bilaterally, lingual to the mandibular premolars (Fig. 44.16).

Toxic epidermal necrolysis (TEN; Lyell’s disease).

A rare clinicopathological entity, with a high mortality, characterized by extensive detachment of full-thickness epithelium. The distinction from erythema multiforme is unclear, but most cases of TEN are drug-induced and the lesions are extremely widespread.



Fig. 44.14 Attrition



Fig. 44.15 Torus palatinus

Drugs appear to trigger what appears to be an immunologically related reaction with sub- and intraepithelial vesiculation. Recently, an increased number of cases in HIV/AIDS patients has been recorded. TEN presents with a cough, sore throat, burning eyes, malaise and low fever, followed after about 1–2 days by skin and mucous membrane lesions. The entire skin surface and oral mucosae may be involved, with up to 100% sloughing off. Oral mucosae are involved in almost all cases. Gingival lesions are common and clinically are inflamed, with blister formation leading to painful widespread erosions.

Sheet-like loss of the epithelium and a positive Nikolsky sign are characteristic. Biopsy of perilesional tissue, with histological and immunostaining examination are essential to the diagnosis. Histopathological examination is characteristic, showing necrosis of the whole epithelium detached from the lamina propria. Patients with TEN must be admitted to a hospital intensive care unit as soon as possible for management.

Toxoplasmosis. Infection by the parasite *Toxoplasma gondii*, which infests members of the cat family who excrete it in faeces. *T. gondii* survives in soil for up to 1 year, and infection is generally by ingestion of cysts or oocysts, which are present in up to 10% of lamb and 25% of pork used for human consumption. In



Fig. 44.16 Torus mandibularis

normal healthy patients symptomatic toxoplasmosis manifests as:

- glandular fever syndrome, with a negative Paul-Bunell test
- ocular toxoplasmosis with chorioretinitis.

Transplacental transmission may result in fetal defects.

In immunocompromised patients such as those with HIV/AIDS, *T. gondii* may produce CNS involvement. Toxoplasmosis is diagnosed by detection of serum antibodies by the Sabin–Feldmann dye test, indirect haemagglutination or IgM fluorescent antibody tests, and isolation of *T. gondii* or histological demonstration of trophozoites. Toxoplasmosis is treated with pyrimethamine and sulfadiazine.

Trichodonto-osseous syndrome. Autosomal dominant; kinky hair, amelogenesis imperfecta; taurodont molars and brittle nails.

Tuberculosis. Infection with mycobacteria, usually *Mycobacterium tuberculosis*, but rarely atypical mycobacteria, e.g. *M. avium-intracellulare*, *M. scrofulaceum* and *M. kansasii*, especially in HIV infection. Uncommon, tuberculosis is usually pulmonary and seen mainly in alcoholics, diabetics, patients with immune defects (including HIV infection), and certain racial groups (e.g. Asian). Clinical features may include a single chronic ulcer on the dorsum of tongue associated with (postprimary) pulmonary infection. Diagnosis is confirmed by biopsy, sputum culture, tuberculin testing and chest radiography. Management is with combination chemotherapy. Treatment is started with three drugs in combination in order to minimize the emergence of bacterial resistance, and is then continued with two or more antibiotics, usually from the following: rifampicin, isoniazid, ethambutol or streptomycin. Chemotherapy is usually effective treatment, but must be given for prolonged periods and, if chemotherapy is less than adequate, bacterial resistance readily develops. Multi-drug resistance

(MDR) and highly resistant strains (X DR-TB) are increasing in HIV/AIDS.

Tularemia. Infection by the coccobacillus *Francisella tularensis*. The epidemics are thought to be water-borne. Most patients are young and female. In most of the cases the disease presents itself in oropharyngeal form, with fever and tonsillopharyngitis and cervical lymphadenopathy. Streptomycin is given to most patients in combination with tetracycline, doxycycline or chloramphenicol.

Ulcerative colitis. Inflammatory bowel disease, which may present with persistent diarrhoea and is frequently painless, with passage of blood and mucus in severe cases, iron deficiency anaemia, weight loss, and mucosal pustules (pyostomatitis vegetans), irregular chronic ulcers and aphthae. Diagnosis is by biopsy, full blood picture, sigmoidoscopy and barium enema. Management is with haematinics for any secondary deficiencies; topical corticosteroids may be helpful; as may sulphasalazine, or corticosteroid enemas.

White sponge naevus (pachyderma oralis, white folded gingivostomatitis). Rare autosomal-dominant defect of keratin causing a benign familial disorder with lesions, typically:

- symptomless
- white
- shaggy or folded or wrinkled
- bilateral
- seen in the buccal mucosa.

Lesions are sometimes seen in other oral sites especially the tongue, the floor of the mouth, or elsewhere, or in the:

- nose and upper respiratory tract
- pharynx
- oesophagus
- genitals
- anus.

The family history and examination are usually adequate to make the diagnosis, but there may be confusion with other white lesions, when a biopsy is indicated.

Further reading

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SECTION 6

ADVERSE DRUG REACTIONS

45 Adverse drug reactions 375

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► Box 45.1

Drug-related xerostomia

Drugs most commonly implicated	Drugs occasionally implicated
Alpha receptor antagonists for treatment of urinary retention	Amphetamines
Anticholinergics	Antihistamines
Antidepressants (serotonin agonists, or noradrenaline and/or serotonin re-uptake blockers)	Antihypertensive agents
Antipsychotics such as phenothiazines	Antimigraine agents
Atropinics	Appetite suppressants
Muscarinic receptor antagonists for treatment of overactive bladder	Benzhexol
Protease inhibitors	Benzodiazepines, hypnotics, opioids and drugs of abuse
Radioiodine	Benztropine
	Biperiden
	Bronchodilators
	Clonidine
	Cyclobenzaprine
	Cytokines
	Cytotoxics
	Dideoxyinosine
	Decongestants and 'cold cures'
	Diuretics
	Fenfluramine
	Fluoxetine
	Ganglion-blocking agents
	Histamine 2 antagonists and proton pump inhibitors
	Ipratropium
	Isotretinoin
	Leva-dopa
	Lithium
	Monoamine oxidase
	Omeprazole
	Opiates
	Orphenadrine
	Phenothiazines
	Propantheline
	Retinoids
	Selegiline
	Skeletal muscle relaxants
	Thiabendazole

► Box 45.2

Drug-related salivary gland swelling or pain

Drugs most commonly implicated	Drugs occasionally implicated
Antihypertensives	Anti-thyroid agents
Chlorhexidine	Bretylium
Cytotoxics	Cimetidine
Iodides	Clonidine
	Clozapine
	Deoxycycline
	Famotidine
	Ganglion-blocking agents
	Insulin
	Interferon
	Isoprenaline
	Methyldopa
	Naproxen
	Nifedipine
	Nitrofurantoin
	Oxyphenbutazone
	Phenothiazines
	Phenylbutazone
	Phenytoin
	Ranitidine
	Ritodrine
	Sulfonamides
	Trimepramine

► Box 45.3

Drug-related hypersalivation

Drugs most commonly implicated	Drugs occasionally implicated
Anticholinesterases	Alprazolam
Clozapine	Amiodarone
	Buprenorphine
	Buspirone
	Clonazepam
	Diazoxide
	Ethionamide
	Gentamicin
	Guanethidine
	Haloperidol
	Imipenem/cilastatin
	Iodides
	Kanamycin
	Ketamine
	Lamotrigine
	Leva-Dopa
	Mefenamic acid
	Mercurials
	Nicardipine
	Niridazole
	Pentoxifylline
	Remoxipride
	Risperidone
	Rivastigmine
	Tacrine
	Tobramycin
	Triptorelin
	Venlafaxine
	Zaleplon

► Box 45.4

Drug-related taste abnormalities

Drugs most commonly implicated	Drugs occasionally implicated
Anti-thyroids	Acarbose
Aurothiomalate	Acetazolamide
Aztreonam	Amityptiline
Baclofen	Aspirin
Biguanides	Atrovastatin
Calcitonin	Ceftirizine
Captopril	Cisplatin
Cilazapril	Clidinium
Metronidazole	Clomipramine
Penicillamine	Cocaine
Protease inhibitors	Diazoxide
	Dicyclomine
	Enalapril
	Etidronate
	Fluoxetine
	Fluvoxamine
	Indometacin
	Isotretinoin
	Leva-Dopa
	Losartan
	Pentamidine
	Phenytoin
	Propantheline
	Rifabutin
	Rivastigmine
	Spironolactone
	Topiramate
	Venlafaxine

► Box 45.5

Drug-related oral ulceration

Drugs most commonly implicated	Drugs occasionally implicated
Cytotoxics	Alendronate
Immunosuppressive agents	Aztreonam
NSAIDs, e.g. Indometacin	Aurothiomalate
	Captopril
	Clarithromycin
	Cocaine
	Emepromium
	Gold
	Interferons
	Isoprenaline
	Losartan
	Naproxen
	Nicorandil
	Olanzapine
	Pancreatin
	Penicillamine
	Phenindione
	Phenylbutazone
	Phenytoin
	Potassium chloride
	Proguanil
	Protease inhibitors
	Sertraline
	Sulfonamides

► Box 45.6

Drug-related contact stomatitis (stomatitis venenata)

Drugs most commonly implicated	Drugs occasionally implicated
Anaesthetics	Chewing gum
Antibiotics	Cosmetics
Antiseptics	Dental materials
Barbiturates	
Dentifrices	
Mouthwashes	
Phenacetin	
Sulfonamides	
Tetracyclines	

➤ **Box 45.7****Drug-related lichenoid reactions**

Drugs most commonly implicated	Drugs occasionally implicated
Antihypertensives	Angiotensin converting enzyme inhibitors
Antimalarials	Amiphenazole
NSAIDs	Captopril
	Carbimazole
	Chloroquine
	Chlorpropamide
	Clofibrate
	Dapsone
	Dipyridamole
	Ethionamide
	Gaunoclor
	Gold
	Griseofulvin
	Labetalol
	Lincomycin
	Lithium
	Mepacrine
	Mercury (amalgam)
	Metformin
	Methyldopa
	Metronidazole
	Niridazole
	Oxprenolol
	Para-aminosalicylate
	Penicillamine
	Phenindione
	Phenothiazines
	Practolol
	Propranolol
	Prothionamide
	Quinidine
	Quinine
	Streptomycin
	Tetracycline
	Thiazides
	Tolbutamide
	Triprolidine

➤ **Box 45.8****Drug-related oral candidiasis****Drugs most commonly implicated**

Broad-spectrum antimicrobials
Corticosteroids
Drugs causing xerostomia
Immunosuppressives

➤ **Box 45.9****Drug-related pemphigus-like reactions**

Drugs most commonly implicated	Drugs occasionally implicated
Diclofenac	Captopril
Penicillamine	
Rifampicin	

➤ **Box 45.10****Drug-related erythema multiforme (and Stevens–Johnson syndrome and toxic epidermal necrolysis)**

Drugs most commonly implicated	Drugs occasionally implicated
Allopurinol	Busulphan
Barbiturates	Cephalosporins
Carbamazepine	Chlorpropamide
NSAIDs	Clindamycin
Penicillin	Codeine
Phenytoin	Ethambutol
Sulfonamides	Furosemide
	Gold
	Minoxidil
	Oestrogens
	Phenothiazines
	Phenylbutazone
	Progestogens
	Protease inhibitors
	Rifampicin
	Tetracyclines
	Tolbutamide
	Vancomycin
	Verapamil

► **Box 45.11****Drug-related lupoid reactions**

Drugs most commonly implicated	Drugs occasionally implicated
Hydralazine	Ethosuximide
Procainamide	Gold
	Griseofulvin
	Methyldopa
	Para-aminosalicylate
	Penicillin
	Phenytoin
	Phenothiazines
	Streptomycin
	Sulfonamides
	Tetracyclines
	Isoniazid

► **Box 45.12****Drug-related cheilitis**

Drugs most commonly implicated	Drugs occasionally implicated
Etretinate	Atrovastatin
Indinavir	Busulphan
Isotretinoin	Clofazimine
Protease inhibitors	Clomipramine
Vitamin A	Cyancobalamin
	Gold
	Methyldopa
	Psoralens
	Streptomycin
	Sulfasalazine
	Tetracycline

► **Box 45.13****Drug-related oral mucosal pigmentation**

Drugs most commonly implicated	Drugs occasionally implicated
Amalgam	ACTH
Chlorhexidine	Amiodarone
Smoking/tobacco	Amodiaquine
	Anticonvulsants
	Arsenic
	Betel
	Bismuth
	Bromine
	Busulphan
	Chlorhexidine
	Chloroquine
	Clofazimine
	Coal
	Copper
	Cyclophosphamide
	Doxorubicin
	Gold
	Heroin
	Iron
	Lead
	Manganese
	Mepacrine
	Methyldopa
	Minocycline
	Oral contraceptives
	Phenolphthalein
	Phenothiazines
	Quinacrine
	Quinidine
	Silver
	Thallium
	Tin
	Vanadium
	Zidovudine

► Box 45.14

Drug-related gingival swelling

Drugs most commonly implicated	Drugs occasionally implicated
Amlodipine	Amphetamines
Ciclosporin	Cotrimoxazole
Diltiazem	Erythromycin
Felodipine	Ethosuximide
Lacidipine	Ketoconazole
Nifedipine	Lamotrigine
Oral contraceptives	Lithium
Phenytoin	Phenobarbitone
Verapamil	Primidone
	Sertraline
	Topiramate
	Valproate
	Vigabatrin

► Box 45.15

Drug-related angio-oedema

Drugs most commonly implicated	Drugs occasionally implicated
Angiotensin converting enzyme inhibitors	Aspirin
	Clindamycin
	Droperidol
	Mianserin

► Box 45.16

Drug-related trigeminal paraesthesia or hypoaesthesia

Drugs most commonly implicated	Drugs occasionally implicated
Acetazolamide	Amitriptyline
Articaine	Chlorpropamide
Labetalol	Colistin
Protease inhibitors	Ergotamine
Vincristine	Gonadotropin-releasing hormone analogues
	Hydralazine
	Interferon alpha
	Isoniazid
	Mefloquine
	Methysergide
	Monoamine oxidase inhibitors
	Nalidixic acid
	Nicotinic acid
	Nitrofurantoin
	Pentamidine
	Phenytoin
	Prilocaine
	Propofol
	Propranolol
	Stilbamidine
	Streptomycin
	Sulfonylureas
	Sulthiame
	Tolbutamide
	Tricyclics
	Trilostane

► Box 45.17

Drug-related involuntary facial movements

Drugs most commonly implicated	Drugs occasionally implicated
L-dopa	Butyrophenones
Metoclopramide	Carbamazepine
Phenothiazines	Lithium
	Methyldopa
	Metirosine
	Phenytoin
	Trifluoroperazine

➤ **Box 45.18****Drug-related halitosis**

Drugs most commonly implicated	Drugs occasionally implicated
Drugs causing xerostomia	Dimethyl sulfoxide (DMSO) Disulfiram Isorbide dinitrate

➤ **Box 45.21****Drugs causing extrinsic tooth discolouration**

Drug	Discolouration caused
Chlorhexidine	Yellow/Brown
Oral iron salts	Black
Co-amoxiclav	Yellow or Grey/Brown
Essential oils	Yellow/Brown
Fluoride	Brown

➤ **Box 45.19****Drug-related orofacial pain**

Drugs most commonly implicated	Drugs occasionally implicated
Angiotensin converting enzyme inhibitors Vinca alkaloids	Benzotropine Biperidin Griseofulvin Lithium Penicillins Phenothiazines Stilbamidine Ticarcillin Vitamin A

➤ **Box 45.22****Drug-related intrinsic tooth discolouration**

Drug-related permanent tooth discolouration (intrinsic staining)	Discolouration caused
Fluoride	White/Brown discolouration
Tetracyclines	Yellow > Brown/Grey
Minocycline	Green-gray/blue-grey
Ciprofloxacin	Greenish

➤ **Box 45.20****Drug-related tooth discolouration**

Drugs most commonly implicated	Drugs occasionally implicated
Chlorhexidine Fluorides Iron Tetracyclines	Antibiotics Clarithromycin Enalapril Essential oil Etidronate Fosinopril Imipenem Lisinopril Metronidazole Penicillin Pentamidine Perindopril Propafenone Quinapril Ramipril Terbinafine Trandolopril Zopiclone

► **Box 45.23**

Drugs that may lead to tooth structure damage

Drug	Examples	Possible damage to tooth structure
Sugar-containing oral (liquid) medication	Various	Caries
Drugs that result in decreased salivary secretion (xerostomia)	See Box 45.1	Caries
Drugs with a low pH	Aspirin, anti-asthmatic drugs	Erosion
Drugs causing gastro-oesophageal reflux	Theophylline, anticholinergics, progesterone, calcium channel blockers, anti-asthmatics	Erosion
Drugs inducing bruxism	Dopamine agonists, dopamine antagonists, tricyclic antidepressants, selective serotonin reuptake inhibitors, alcohol, cocaine, amphetamines	Attrition
Drugs used for internal tooth bleaching	Hydrogen peroxide and sodium perborate	Cervical root resorption
Drugs used for treatment of childhood cancers	Cytotoxic agents	Abnormal dental development
Anticonvulsants	Phenytoin	
Fluorides	Any	Fluorosis

► **Box 45.24**

Drug-related osteonecrosis

Bisphosphonates

Further reading

Scully C, Bagan JV 2004 Adverse drug reactions in the orofacial region. Crit Rev Oral Biol Med 15:221–39

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